with ethyl acetate to give product, 550mg., 48%, mp 234-236°C dec.

Elemental Analyses for $C_{21}H_{18}N_2O_3$:

Calculated: C 72.82; H 5.24; N 8.09

Found: C 72.54; H 5.19; N 8.04

C. Preparation of methyl [9-benzyl-4-carbamoyl-7-methoxycarbazol-5-yl]oxyacetic acid.

A solution of 430mg. (1.2 mmol) of the product from Part B in 40mL of dimethylformamide and a few mLs of tetrahydrofuran was treated with 60mg. of sodium hydride (60% in mineral oil; 1.5 mmol) for 15 minutes and then with 0.13mL (1.4 mmol) of methylbromoacetate for 16 hours, diluted with ethyl acetate, washed with water, washed with brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue was chromatographed on silica gel eluting with a gradient dichloromethane/ 1-3% methanol to give title compound, 320mg., 62%, mp 170-172°C.

Elemental Analyses for $C_{24}H_{22}N_2O_5$:

Calculated: C 68.89; H 5.30; N 6.69

Found: C 68.64; H 5.41; N 6.57

D. Preparation of [9-benzyl-4-carbamoyl-7-methoxycarbazol-5-yl]oxyacetic acid sodium salt

To a suspension of 60mg (0.15mmol) of the product from Part C in 30mL of ethanol was added 0.075mL of 2.0 N sodium hydroxide. The mixture was heated until solution, cooled, concentrated *in vacuo*, diluted with ethyl acetate, concentrated *in vacuo*, cooled, and filtered to give product, amorphous solid, 50mg., 80%. MS (FAB+) 427.2 : MS (ion spray) +Q1 405.5, -Q1 403.5

Example 6

Preparation of 9-benzyl-7-methoxy-5-cyanomethyloxy-1,2,3,4-tetrahydrocarbazole-4-carboxamide

A solution of 1.47gram (4.19 mmol) of the product from Example 3, Part A in 146ml. of dimethylformamide and 31ml. tetrahydrofuran was treated with 210mg. of sodium hydride (60% in mineral oil; 5.24mmol) for 10 minutes and then with 0.39ml. (0.66 mmol) of bromoacetonitrile for 3.5 hours. The mixture was diluted with ethyl acetate, washed with water, washed with brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue was chromatographed on silica gel eluting with a gradient of 0 to 4% methanol in methylene chloride to give the titled product, 1.34gram, 82%.

Elemental analysis for $C_{23}H_{23}N_3O_3$:

Calculated:	C 70.93; H 5.95; N 10.79
Theory:	C 70.67; H 6.06; N 10.83

Example 7

Preparation of 9-benzyl-7-methoxy-5-(1H-tetrazol-5-yl-methyl)oxy)-1,2,3,4-tetrahydrocarbazole-4-carboxamide

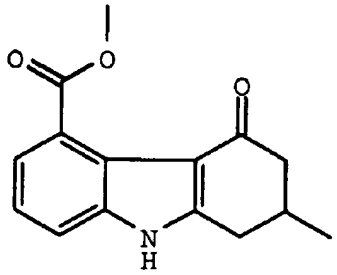
A portion of the compound of Example 6, 0.45gram (1.16mmol) was heated with 5ml. tri-n-butyl in hydride at 95°C for 1 hour. The reaction was then added to a mixture of 125 ml. acetonitrile, 25ml. tetrahydrofuran, and 50ml. acetic acid and stirred for 2 hours. The mixture was extracted 4 times with hexane and the residue evaporated *in vacuo*. Crystallization from acetone and hexane afforded the titled compound, 0.30gram, 60%.

Elemental analysis for $C_{23}H_{24}N_6O_3$:

Calculated:	C 63.88; H 5.59; N 19.43
Theory:	C 64.06; H 5.64; N 19.28

Preparation 1

Preparation of 5-Carbomethoxy-1,2-dihydro-2-methyl-9H-carbazol-4(3H)-one from 2-bromo-3-nitrobenzoic acid



a) Methyl 2-bromo-3-nitrobenzoate

A solution of 2-bromo-3-nitrobenzoic acid (28.4 g, 115.0 mM), iodomethane (18.0 g, 127 mM), and potassium carbonate (19.0 g, 137.4 mM) in 100 mL dimethylformamide was stirred at room temperature for 72 hours. The mixture was poured into 1.5 liters of water. The resultant precipitate was collected by filtration and dried *in vacuo* to afford 28.79 g (96%) of methyl 2-bromo-3-nitrobenzoate as a white solid. ^{1}H NMR (DMSO-d6) δ 8.3 (dd, 1H, J=1 and 8 Hz), 7.9 (dd, 1H, J=1 and 8 Hz), 7.7 (t, 1H, J=8 Hz), and 3.9 (s, 3H). IR (KBr, cm^{-1}) 2950, 1738, 1541, 1435, 1364, 1298, and 1142. MS (FD) m/e 259, 261.

Elemental Analyses for $C_8H_6NO_4Br$:

Calculated: C, 36.95; H, 2.33; N, 5.39.

Found: C, 37.14; H, 2.37; N, 5.45.

b) Methyl 2-bromo-3-aminobenzoate

Hydrogen gas was passed through a solution of methyl 2-bromo-3-nitrobenzoate (0.20 g, 0.77 mM) and 0.1 g of 3% sulfided platinum on carbon in 25 mL ethyl acetate for 24 hours at room temperature. The catalyst was removed by filtration through celite. Concentration of the filtrate afforded 0.175 g (99%) of methyl 2-bromo-3-aminobenzoate as

a yellow oil. ^{1}H NMR ($CDCl_3$) δ 7.15 (t, 1H, J=8 Hz), 7.1 (dd, 1H, J=1 and 8 Hz), 6.8 (dd, 1H, J=1 and 8 Hz), and 3.95 (s, 3H). IR ($CHCl_3$, cm^{-1}) 3550, 3380, 2980, 2900, 1729, 1613, 1465, 1451, 1434, 1324, 1266, and 1025. MS (FD) m/e 230, 232.

Elemental Analyses for $C_8H_8NO_2Br$:

Calculated: C, 41.77; H, 3.51; N, 6.09.

Found: C, 42.01; H, 3.29; N, 6.00.

c) 3-(3-Carbomethoxy-2-bromoanilino)-5-methyl-cyclohex-2-en-1-one

A mixture of methyl 2-bromo-3-aminobenzoate (10.2 g, 44.3 mM) and 5-methyl-1,3-cyclohexanedione (6.15 g, 48.7 mM) was heated at 125 °C under a stream of nitrogen for 1.5 hours. The resultant solid was triturated with ethyl acetate to afford 9.98 g (67%) of 3-(3-carbomethoxy-2-bromoanilino)-5-methyl-cyclohex-2-en-1-one. ^{1}H NMR ($CDCl_3$) δ 7.55 (m, 2H), 7.35 (dd, J=8 and 8 Hz, 1H), 6.4 (bs, 1H), 5.55 (s, 1H), 3.95 (s, 3H), 2.6-2.0 (m, 5H), 1.15 (d, J=7 Hz, 3H). MS (ES) m/e 338, 340.

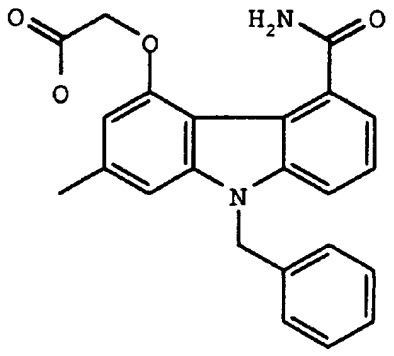
d) 5-Carbomethoxy-1,2-dihydro-2-methyl-9H-carbazol-4(3H)-one

A suspension of 3-(3-carbomethoxy-2-bromoanilino)-5-methyl-cyclohex-2-en-1-one (9.98 g, 29.5 mM), palladium acetate (0.66 g, 2.95 mM), tri-*o*-tolylphosphine (1.8 g, 5.9 mM), and triethylamine (5.10 ml, 36.6 mM) in 75 mL acetonitrile was heated at reflux for 3 hours. The solvent was removed *in vacuo*. The residue was dissolved in methylene chloride, washed with 1 N HCl, then with saturated brine, dried over anhydrous sodium sulfate, filtered, and concentrated to afford 11 g of crude product. Purification by HPLC on silica gel (elution with gradient methylene chloride/ethyl acetate) afforded 5.7 g (75%) of 5-

carbomethoxy-1,2-dihydro-2-methyl-9H-carbazol-4(3H)-one. ^{1}H NMR ($CDCl_3$) δ 9.5 (bs, 1H), 7.4 (d, J=8 Hz, 1H), 7.35 (d, J=8 Hz, 1H), 7.2 (dd, J=8 and 8 Hz, 1H), 4.0 (s, 3H), 2.9 (dd, J=13 and 4 Hz, 1H), 2.55 (m, 2H), 2.4 (m, 1H), 2.25 (dd, J=15 and 9 Hz, 1H), 1.05 (d, J=7 Hz, 3H). MS (ES) m/e 226, 258.

EXAMPLE 8

Preparation of {9-[(phenyl)methyl]-5-carbamoyl-2-methyl-carbazol-4-yl}oxyacetic acid



A. 9-[(Phenyl)methyl]-5-carbomethoxy-2-methyl-1,2-dihydrocarbazol-4(3H)-one

A suspension of 5-carbomethoxy-1,2-dihydro-2-methyl-9H-carbazol-4(3H)-one (2.0 g, 7.77 mM), benzyl bromide (0.94 ml, 7.93 mM), and potassium carbonate (2.15 g, 15.5 mM) in 39 mL DMF was stirred at room temperature for 22 hours. The mixture was diluted with ethyl acetate and 1N HCl. The layers were separated and the aqueous layer extracted with ethyl acetate. The combined ethyl acetate layers were extracted with 1N HCl twice, once with water and once with brine. After drying ($NaSO_4$), evaporation *in vacuo* afforded 2.61g (97%) of 9-[(phenyl)methyl]-5-carbomethoxy-2-methyl-1,2-dihydrocarbazol-4(3H)-one. ^{1}H NMR ($CDCl_3$) δ 7.6-7.4 (m, 6H), 7.0 (m, 2H), 5.4 (s, 2H), 4.05 (s, 3H), 3.0 (m, 1H),

2.65-2.45 (m, 3H), 2.3 (dd, J=15 and 9 Hz, 1H), 1.1 (d, J=7 Hz, 3H). MS (ES) m/e 316, 348.

B. 9-[(Phenyl)methyl]-2-methyl-4-hydroxy-5-carbomethoxy carbazole

A solution of the 9-[(phenyl)methyl]-5-carbomethoxy-2-methyl-1,2-dihydrocarbazol-4(3H)-one (1.30 g, 3.74 mM) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.93 g, 4.12 mM) in 37 mL of toluene was stirred between 80-90 °C for 5 hours. The mixture was purified by column chromatography on silica gel (elution with methylene chloride) to afford 270 mg (21%) of the 9-[(phenyl)methyl]-2-methyl-4-hydroxy-5-carbomethoxy carbazole. ^{1}H NMR ($CDCl_3$) δ 10.45 (s, 1H), 8.0 (d, J=8 Hz, 1H), 7.55 (d, J=8 Hz, 1H), 7.4 (dd, J=8 and 8 Hz, 1H), 7.3 (m, 3H), 7.05 (m, 2H), 6.65 (s, 1H), 6.6 (s, 1H), 5.5 (s, 2H), 4.1 (s, 3H), 2.45 (s, 3H). MS (ES) m/e 314, 346.

C. 9-[(Phenyl)methyl]-2-methyl-4-hydroxy-5-carbamoyl carbazole

A solution of the 9-[(phenyl)methyl]-2-methyl-4-hydroxy-5-carbomethoxy carbazole (470 mg, 1.36 mM) in 20 ml THF and 80 mL concentrated aqueous ammonium hydroxide was sonicated for 6 hours at 30-40 °C. The precipitated solid was filtered and triturated with Et_2O to afford 200 mg (44%) of 9-[(phenyl)methyl]-2-methyl-4-hydroxy-5-carbamoyl carbazole. ^{1}H NMR (DMSO-d6) δ 10.5 (s, 1H), 8.8 (bs, 1H), 8.4 (bs, 1H), 7.75 (m, 1H), 7.4 (m, 2H), 7.25 (m, 3H), 7.1 (m, 2H), 6.95 (s, 1H), 6.45 (s, 1H), 5.65 (s, 2H), 2.4 (s, 3H). MS (ES) m/e 314, 331.

D. {9-[(Phenyl)methyl]-2-methyl-5-carbamoylcarbazol-4-yl}oxyacetic acid, methyl ester

60% Sodium hydride in mineral oil (30.4 mg, 0.76 mM) was added to a solution of 9-[(phenyl)methyl]-2-methyl-4-hydroxy-5-carbamoyl carbazole (202 mg, 0.61 mM) in 21 mL DMF and 4.6 ml THF. After 10 minutes, methyl bromoacetate (77 µl, 0.482 mM) was added and the resultant mixture stirred at room temperature for 1.25 hours. The mixture was diluted with ethyl acetate and washed with H_2O. The aqueous layer was extracted with ethyl acetate. The combined organic layers were extracted with saturated brine, dried over sodium sulfate, filtered, and concentrated. The residue was purified by column chromatography on silica gel (elution with ethyl acetate) to afford 184 mg (75%) of {9-[(phenyl)methyl]-2-methyl-5-carbamoylcarbazol-4-yl}oxyacetic acid, methyl ester. ^{1}H NMR (DMSO-d6) δ 7.55 (d, 1H, J=8 Hz), 7.5 (bs, 1H), 7.4-7.15 (m, 9H), 6.45 (s, 1H), 5.7 (s, 2H), 4.9 (s, 2H), 3.75 (s, 3H), 2.4 (s, 3H). MS (FD) m/e 386, 403.

Elemental Analyses for $C_{24}H_{22}N_2O_4$:

Calculated:	C, 71.63; H, 5.51; N, 6.96.
Found:	C, 71.74; H, 5.81; N, 6.69.

E. {9-[(Phenyl)methyl]-2-methyl-5-carbamoylcarbazol-4-yl}oxyacetic acid

A solution of the {9-[(phenyl)methyl]-2-methyl-5-carbamoylcarbazol-4-yl}oxyacetic acid, methyl ester (83.5 mg, 0.207 mM) and 1.0 mL (2.0 mM) of 2 N NaOH in 10 mL of ethanol was stirred for 45 minutes at 25 °C. The resultant white precipitate was collected by filtration, washed with a small amount of EtOH, then dried *in vacuo* to afford 48 mg (56%) of the {9-[(phenyl)methyl]-2-methyl-5-carbamoylcarbazol-4-yl}oxyacetic acid sodium salt as a white powder. MS (ES) m/e 314, 372, 389, 411. The filtrate was

acidified with 1N HCl to pH =1. After cooling to 5°C, the resultant white precipitate was collected by filtration, washed with water, then dried *in vacuo* to afford 24 mg (29%) {9-[(phenyl)methyl]-2-methyl-5-carbamoylcarbazol-4-yl}oxyacetic acid. ^{1}H NMR (DMSO-d6) δ 11.2 (bs, 1H), 7.8 (bs, 1H), 7.6 (d, J=8 Hz, 1H), 7.45 (bs, 1H), 7.4-7.05 (m, 8H), 6.45 (s, 1H), 5.65 (s, 2H), 4.9 (s, 2H), 2.4 (s, 3H). MS (ES) m/e 314, 372, 389.

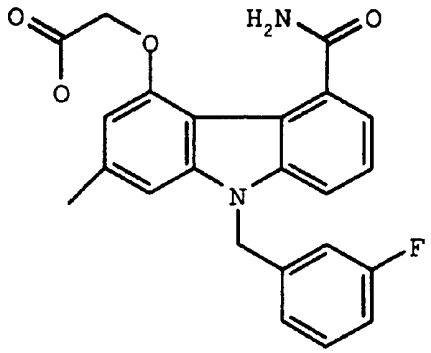
Elemental Analyses for $C_{23}H_{20}N_2O_4$:

Calculated: C, 71.12; H, 5.19; N, 7.21.

Found: C, 71.33; H, 5.47; N, 7.19.

EXAMPLE 9

Preparation of {9-[(3-fluorophenyl)methyl]-5-carbamoyl-2-methyl-carbazol-4-yl}oxyacetic acid



A. 9-[(3-Fluorophenyl)methyl]-5-carbomethoxy-2-methyl-1,2-dihydrocarbazol-4(3H)-one

A suspension of 5-carbomethoxy-1,2-dihydro-2-methyl-9H-carbazol-4(3H)-one (1.0 g, 3.89 mM), 3-fluorobenzyl bromide (0.48 ml, 3.97 mM), and potassium carbonate (1.07 g, 7.78 mM) in 20 mL DMF was stirred at room temperature for 22 hours. The mixture was diluted with EtOAc and 1N HCl. The layers were separated and the aqueous extracted with EtOAc. The combined EtOAc layers were extracted with 1N HCl, water, then brine. After drying (Na_2SO_4), evaporation *in vacuo*

afforded 1.38g (97%) of the 9-[(3-fluorophenyl)methyl]-5-carbomethoxy-2-methyl-1,2-dihydrocarbazol-4(3H)-one. ^{1}H NMR ($CDCl_3$) δ 7.4-7.2 (m, 5H), 7.0 (m, 1H), 6.75 (m, 2H), 5.4 (s, 2H), 4.05 (s, 3H), 3.0 (m, 1H), 2.65-2.45 (m, 3H), 2.3 (dd, J=15 and 9 Hz, 1H), 1.1 (d, J=7 Hz, 3H). MS (ES) m/e 334, 366.

B. 9-[(3-Fluorophenyl)methyl]-2-methyl-4-hydroxy-5-carbomethoxy carbazole

A solution of the 9-[(3-fluorophenyl)methyl]-5-carbomethoxy-2-methyl-1,2-dihydrocarbazol-4(3H)-one (1.37 g, 3.75 mM) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.94 g, 4.13 mM) in 38 mL of toluene was stirred between 80-90 °C for 3 hours. The mixture was purified by column chromatography on silica gel (elution with methylene chloride) to afford 0.33 g (24%) of 9-[(3-fluorophenyl)methyl]-2-methyl-4-hydroxy-5-carbomethoxy carbazole. ^{1}H NMR ($CDCl_3$) δ 10.45 (s, 1H), 8.0 (d, J=8 Hz, 1H), 7.55 (d, J=8 Hz, 1H), 7.4 (dd, J=8 and 8 Hz, 1H), 7.3 (m, 2H), 6.95 (m, 1H), 6.85 (d, J=8 Hz, 1H), 6.75 (m, 1H), 6.65 (s, 1H), 5.5 (s, 2H), 4.1 (s, 3H), 2.45 (s, 3H). MS (ES) m/e 332, 364.

C. 9-[(3-Fluorophenyl)methyl]-2-methyl-4-hydroxy-5-carbamoyl carbazole

A solution of the 9-[(3-fluorophenyl)methyl]-2-methyl-4-hydroxy-5-carbomethoxy carbazole (0.33 g, 0.91 mM) in 14 ml THF and 54 mL concentrated aqueous ammonium hydroxide was sonicated for 6.5 h at 30-40 °C. The precipitated solid was filtered, washed with water, and triturated with 35 ml Et_2O to afford 182 mg (57%) of 9-[(3-fluorophenyl)methyl]-2-methyl-4-hydroxy-5-carbamoyl carbazole. ^{1}H NMR (DMSO-d6) δ 10.5 (s, 1H), 8.8 (bs, 1H), 8.4 (bs, 1H), 7.75 (m, 1H), 7.4 (m, 2H), 7.25 (m, 1H), 7.05 (m, 1H), 6.9 (m, 2H), 6.85 (d,

J=8 Hz, 1H), 6.45 (s, 1H), 5.65 (s, 2H), 2.4 (s, 3H). MS (ES) m/e 332, 349.

D. {9-[(3-Fluorophenyl)methyl]-2-methyl-5-carbamoylcarbazol-4-yl}oxyacetic acid, methyl ester

60% Sodium hydride in mineral oil (25.9 mg, 0.65 mM) was added to a solution of 9-[(3-fluorophenyl)methyl]-2-methyl-4-hydroxy-5-carbamoyl carbazole (181 mg, 0.52 mM) in 18 mL DMF and 3.9 ml THF. After 10 minutes, methyl bromoacetate (66 µl, 0.70 mM) was added and the resultant mixture stirred at room temperature for 1.25 hours. The mixture was diluted with ethyl acetate and washed with H_2O. The aqueous layer was extracted with ethyl acetate. The combined organic layers were extracted with saturated brine, dried over sodium sulfate, filtered, and concentrated. The residue was purified by column chromatography on silica gel (elution with methylene chloride/acetone gradient) to afford 170 mg (78%) of the {9-[(3-fluorophenyl)methyl]-2-methyl-5-carbamoylcarbazol-4-yl}oxyacetic acid, methyl ester. ^{1}H NMR (DMSO-d6) δ 7.55 (d, 1H, J=8 Hz), 7.5 (bs, 1H), 7.4-7.25 (m, 2H), 7.2 (bs, 1H), 7.05 (m, 3H), 6.95 (d, J=8 Hz, 1H), 6.9 (d, J=8 Hz), 6.45 (s, 1H), 5.65 (s, 2H), 4.9 (s, 2H), 3.75 (s, 3H), 2.4 (s, 3H). MS (FD) m/e 404, 421.

Elemental Analyses for $C_{24}H_{21}FN_2O_4$:

Calculated: C, 68.56; H, 5.03; N, 6.66.

Found: C, 67.75; H, 4.95; N, 6.33.

E. {9-[(3-Fluorophenyl)methyl]-2-methyl-5-carbamoylcarbazol-4-yl}oxyacetic acid

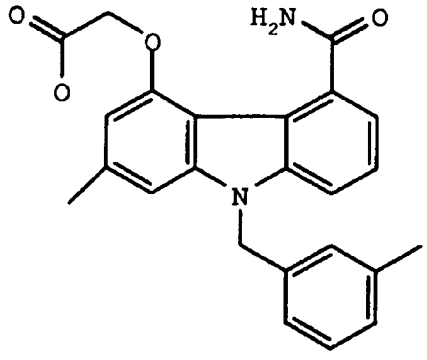
A solution of {9-[(3-fluorophenyl)methyl]-2-methyl-5-carbamoylcarbazol-4-yl}oxyacetic acid, methyl ester (68.3 mg, 0.162 mM) and 0.81 mL (1.6 mM) of 2 N NaOH in 8.1 mL of ethanol was stirred for 30 minutes at 25 °C. The resultant white precipitate was collected by filtration, washed with a

small amount of EtOH, then dried *in vacuo* to afford 11 mg (16%) of {9-[(3-fluorophenyl)methyl]-2-methyl-5-carbamoylcarbazol-4-yl}oxyacetic acid, sodium salt as a white powder. The filtrate was acidified with 1N HCl to pH =2. After cooling to 5°C, the resultant white precipitate was collected by filtration, washed with water, then dried *in vacuo* to afford 31 mg (47%) {9-[(3-fluorophenyl)methyl]-2-methyl-5-carbamoylcarbazol-4-yl}oxyacetic acid. ^{1}H NMR (DMSO-d6) δ 7.75 (bs, 1H), 7.6 (d, 1H, J=8 Hz), 7.45 (bs, 1H), 7.4-7.25 (m, 2H), 7.05 (m, 3H), 6.95 (d, J=8 Hz, 1H), 6.9 (d, J=8 Hz, 1H), 6.45 (s, 1H), 5.65 (s, 2H), 4.8 (s, 2H), 2.4 (s, 3H). MS (ES) m/e 390, 407. Recrystallization from acetone/hexane provided an analytical sample:
Elemental Analyses for $C_{23}H_{19}FN_2O_4$:

Calculated: C, 67.97; H, 4.71; N, 6.89.
Found: C, 68.21; H, 4.93; N, 7.16.

EXAMPLE 10

Preparation of {9-[(3-methylphenyl)methyl]-5-carbamoyl-2-methyl-carbazol-4-yl}oxyacetic acid



A. 9-[(3-Methylphenyl)methyl]-5-carbomethoxy-2-methyl-1,2-dihydrocarbazol-4(3H)-one

A suspension of 5-carbomethoxy-1,2-dihydro-2-methyl-9H-carbazol-4(3H)-one (1.0 g, 3.89 mM), 3-methylbenzyl bromide

(0.54 ml, 3.97 mM), and potassium carbonate (1.07 g, 7.78 mM) in 20 mL DMF was stirred at room temperature for 19 hours. The mixture was diluted with EtOAc and 1N HCl. The layers were separated and the aqueous layer extracted with EtOAc. The combined EtOAc layers were extracted with 1N HCl, water, then brine. After drying ($NaSO_4$), evaporation *in vacuo* afforded 1.41g (100%) of 9-[(3-methylphenyl)methyl]-5-carbomethoxy-2-methyl-1,2-dihydrocarbazol-4(3H)-one. ^1H NMR ($CDCl_3$) δ 7.4-7.05 (m, 6H), 6.8 (m, 1H), 5.3 (s, 2H), 4.05 (s, 3H), 3.0 (m, 1H), 2.7-2.3 (m, 4H), 2.3 (s, 1H), 1.2 (d, J=7 Hz, 3H). MS (ES) m/e 362.

B. 9-[(3-Methylphenyl)methyl]-2-methyl-4-hydroxy-5-carbomethoxy carbazole

To a solution of 9-[(3-methylphenyl)methyl]-5-carbomethoxy-2-methyl-1,2-dihydrocarbazol-4(3H)-one (1.41 g, 3.89 mM) in 13 ml dioxane was added 60% sodium hydride in mineral oil (0.36 g, 8.95 mM). The reaction was stirred 6 minutes, then methyl benzenesulfinate (0.81 ml, 6.22 mM) was added. The reaction was stirred an additional 6 hours, then diluted with 20 ml dioxane and 0.51 ml acetic acid. The mixture was refluxed 30 minutes, diluted with ethyl acetate, and extracted with saturated $NaHCO_3$, brine, then water. After drying ($NaSO_4$), evaporation *in vacuo* afforded 2.30g. The mixture was purified by column chromatography on silica gel (elution with toluene/methylene chloride) to afford 0.92 g (66%) of 9-[(3-methylphenyl)methyl]-2-methyl-4-hydroxy-5-carbomethoxy carbazole. ^1H NMR ($CDCl_3$) δ 10.45 (s, 1H), 8.0 (d, J=8 Hz, 1H), 7.55 (d, J=8 Hz, 1H), 7.4 (dd, J=8 and 8 Hz, 1H), 7.4 (dd, J=8 and 8 Hz, 1H), 7.05 (d, J=8 HZ, 1H), 6.9 (s, 1H), 6.85 (d, J=8 Hz, 1H), 6.75 (s, 1H), 6.7 (s, 1H), 5.45 (s, 2H), 4.1 (s, 3H), 2.4 (s, 3H), 2.25 (s, 3H). MS (ES) m/e 328, 360.

C. 9-[(3-Methylphenyl)methyl]-2-methyl-4-hydroxy-5-carbamoyl carbazole

A solution of 9-[(3-methylphenyl)methyl]-2-methyl-4-hydroxy-5-carbomethoxy carbazole (0.92 g, 2.56 mM) in 38 ml THF and 154 mL concentrated aqueous ammonium hydroxide was sonicated for 6 h at 30-40 °C. The precipitated solid was filtered, washed with water to afford 0.55g (63%) of 9-[(3-methylphenyl)methyl]-2-methyl-4-hydroxy-5-carbamoyl carbazole. ^{1}H NMR (DMSO-d6) δ 10.5 (s, 1H), 8.8 (bs, 1H), 8.4 (bs, 1H), 7.75 (m, 1H), 7.4 (m, 2H), 7.15 (dd, J=8 and 8 Hz, 1H), 7.05 (m, 1H), 7.0 (s, 1H), 6.9 (s, 1H), 6.8 (d, J=8 Hz, 1H), 6.45 (s, 1H), 5.65 (s, 2H), 2.4 (s, 3H), 2.2 (s, 3H). MS (ES) m/e 328, 345.

D. {9-[(3-Methylphenyl)methyl]-2-methyl-5-carbamoylcarbazol-4-yl}oxyacetic acid, methyl ester

60% Sodium hydride in mineral oil (79.8 mg, 2.0 mM) was added to a solution of 9-[(3-methylphenyl)methyl]-2-methyl-4-hydroxy-5-carbamoyl carbazole (0.55 g, 1.60 mM) in 56 mL DMF and 12 ml THF. After 10 minutes, methyl bromoacetate (0.20 ml, 2.16 mM) was added and the resultant mixture stirred at room temperature for 1 hour. The mixture was diluted with ethyl acetate and washed with H_2O. The aqueous layer was extracted with ethyl acetate. The combined organic layers were extracted with saturated brine, dried over sodium sulfate, filtered, and concentrated. The residue was purified by column chromatography on silica gel (elution with methylene chloride/acetone gradient) to afford 0.51 g (76%) of {9-[(3-methylphenyl)methyl]-2-methyl-5-carbamoylcarbazol-4-yl}oxyacetic acid, methyl ester. ^{1}H NMR (DMSO-d6) δ 7.5 (m, 2H), 7.35 (dd, J=8 and 8 Hz, 1H), 7.2-7.1 (m, 2H), 7.05-6.95 (m, 4H), 6.85 (d, J=8 Hz, 1H), 6.45

(s, 1H), 5.6 (s, 2H), 4.9 (s, 2H), 3.75 (s, 3H), 2.4 (s, 3H), 2.2 (s, 3H). MS (FD) m/e 400, 417.

Elemental Analyses for $C_{25}H_{24}N_2O_4$:

Calculated: C, 72.10; H, 5.81; N, 6.73.

Found: C, 71.94; H, 5.71; N, 6.96.

E. {9-[(3-Methylphenyl)methyl]-2-methyl-5-carbamoylcarbazol-4-yl}oxyacetic acid

A solution of {9-[(3-methylphenyl)methyl]-2-methyl-5-carbamoylcarbazol-4-yl}oxyacetic acid, methyl ester (0.12 g, 0.288 mM) and 1.4 mL (2.8 mM) of 2 N NaOH in 14 mL of ethanol was stirred for 30 minutes at 25 °C. The reaction was acidified with 1N HCl to pH =2. After stirring 1 hour, the resultant white precipitate was collected by filtration, washed with water, then dried *in vacuo* to afford 114 mg (95%) {9-[(3-methylphenyl)methyl]-2-methyl-5-carbamoylcarbazol-4-yl}oxyacetic acid. ^{1}H NMR (DMSO-d6) δ 11.1 (bs, 1H), 7.75 (bs, 1H), 7.6 (d, J=8 Hz, 1H), 7.45 (bs, 1H), 7.35 (dd, J=8 and 8Hz, 1H), 7.2-7.0 (m, 5H), 6.85 (d, J=8Hz, 1H), 6.45 (s, 1H), 5.6 (s, 2H), 4.8 (s, 2H), 2.4 (s, 3H), 2.2 (s, 3H). MS (ES) m/e 386, 403. Recrystallization from acetone/hexane provided an analytical sample:

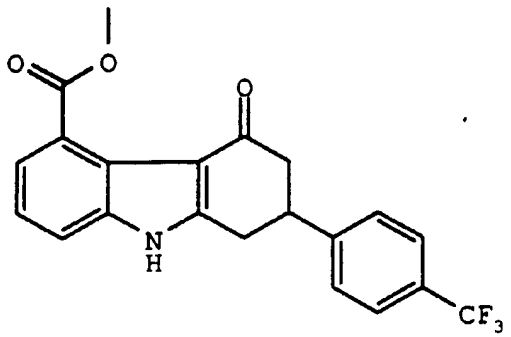
Elemental Analyses for $C_{24}H_{22}N_2O_4$:

Calculated: C, 71.63; H, 5.51; N, 6.96.

Found: C, 71.88; H, 5.65; N, 7.20.

Preparation 2

Preparation of 5-Carbomethoxy-1,2-dihydro-2-(4-trifluoromethylphenyl)-9H-carbazol-4(3H)-one from 2-bromo-3-nitrobenzoic acid



a) Methyl 2-bromo-3-nitrobenzoate

A solution of 2-bromo-3-nitrobenzoic acid (28.4 g, 115.0 mM), iodomethane (18.0 g, 127 mM), and potassium carbonate (19.0 g, 137.4 mM) in 100 mL DMF was stirred at room temperature for 72 hours. The mixture was poured into 1.5 liters of H_2O. The resultant precipitate was collected by filtration and dried *in vacuo* to afford 28.79 g (96%) of methyl 2-bromo-3-nitrobenzoate as a white solid. ^1H NMR (DMSO-d6) δ 8.3 (dd, 1H, J=1 and 8 Hz), 7.9 (dd, 1H, J=1 and 8 Hz), 7.7 (t, 1H, J=8 Hz), and 3.9 (s, 3H). IR (KBr, cm^{-1}) 2950, 1738, 1541, 1435, 1364, 1298, and 1142. MS (FD) m/e 259, 261.

Elemental Analyses for $C_8H_6NO_4Br$:

Calculated: C, 36.95; H, 2.33; N, 5.39.

Found: C, 37.14; H, 2.37; N, 5.45.

b) Methyl 2-bromo-3-aminobenzoate

Hydrogen gas was passed through a solution of methyl 2-bromo-3-nitrobenzoate (0.20 g, 0.77 mM) and 0.1 g of 3% sulfided platinum on carbon in 25 mL ethyl acetate for 24 hours at room temperature. The catalyst was removed by filtration through celite. Concentration of the filtrate

afforded 0.175 g (99%) of methyl 2-bromo-3-aminobenzoate as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 7.15 (t, 1H, J=8 Hz), 7.1 (dd, 1H, J=1 and 8 Hz), 6.8 (dd, 1H, J=1 and 8 Hz), and 3.95 (s, 3H). IR ($CHCl_3$, cm^{-1}) 3550, 3380, 2980, 2900, 1729, 1613, 1465, 1451, 1434, 1324, 1266, and 1025. MS (FD) m/e 230, 232.

Elemental Analyses for $C_8H_8NO_2Br$:

Calculated: C, 41.77; H, 3.51; N, 6.09.

Found: C, 42.01; H, 3.29; N, 6.00.

c) 3-(3-Carbomethoxy-2-bromoanilino)-5-(4-trifluoromethylphenyl-cyclohex-2-en-1-one

A mixture of methyl 2-bromo-3-aminobenzoate (10.2 g, 44.3 mM) and 5-(4-trifluoromethylphenyl)-1,3-cyclohexanedione (1.77 g, 6.93 mM) was heated at 150 °C under a stream of nitrogen for 20 minutes. The resultant solid was triturated with 4:1 EtOAc/Et_2O to afford 2.18 g (74%) of 3-(3-carbomethoxy-2-bromoanilino)-5-(4-trifluoromethylphenyl)-cyclohex-2-en-1-one. ^{1}H NMR (DMSO-d6) δ 8.9 (s, 1H), 7.75-7.5 (m, 7H), 3.9 (s, 3H), 3.5 (m, 1H), 2.9 (dd, J=14 and 9 Hz, 1H), 2.7 (dd, J=14 and 4 Hz, 1H), 2.55 (dd, J=14 and 9 Hz, 1H), 2.35 (dd, J=14 and 4 Hz, 1H). MS (ES) m/e 368, 370.

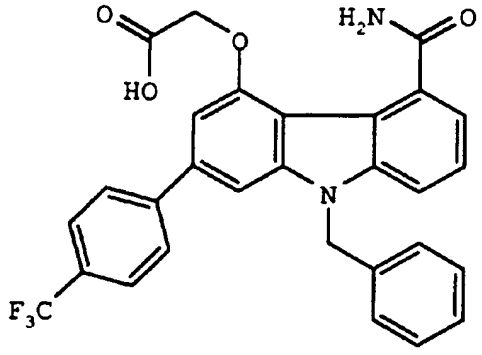
d) 5-Carbomethoxy-1,2-dihydro-2-(4-trifluoromethylphenyl)-9H-carbazol-4(3H)-one

A suspension of 3-(3-carbomethoxy-2-bromoanilino)-5-(4-trifluoromethylphenyl)-cyclohex-2-en-1-one (2.18 g, 4.66 mM), palladium acetate (0.10 g, 0.47 mM), tri-o-tolylphosphine (0.28 g, 0.93 mM), and triethylamine (0.8 ml, 5.78 mM) in 12 mL acetonitrile was heated at reflux for 3 hours. The solvent was removed *in vacuo*. The residue was dissolved in methylene chloride, washed with 1 N HCl, then with saturated brine, dried over anhydrous sodium sulfate,

filtered, and concentrated to afford 2.21 g. Purification by HPLC on silica gel (elution with gradient methylene chloride/ethyl acetate) afforded 1.57 g (87%) of the 5-carbomethoxy-1,2-dihydro-2-(4-trifluoromethylphenyl)-9H-carbazol-4(3H)-one. ^{1}H NMR ($CDCl_3$) δ 9.2 (bs, 1H), 7.6 (d, J=8 Hz, 2H), 7.45-7.35 (m, 5H), 7.25 (d, J=8 Hz, 2H), 3.55 (m, 1H), 3.2-3.0 (m, 2H), 2.7 (m, 2H). MS (ES) m/e 356,388.

EXAMPLE 11

Preparation of {9-[(phenyl)methyl]-5-carbamoyl-2-(4-trifluoromethylphenyl)-carbazol-4-yl}oxyacetic acid



a) 9-[(Phenyl)methyl]-5-carbomethoxy-2-(4-trifluoromethylphenyl)-1,2-dihydrocarbazol-4(3H)-one

A suspension of 5-carbomethoxy-1,2-dihydro-2-(4-trifluoromethylphenyl)-9H-carbazol-4(3H)-one (1.57 g, 4.05 mM), benzyl bromide (0.49 ml, 4.13 mM), and potassium carbonate (1.12 g, 8.10 mM) in 20 mL DMF was stirred at room temperature for 22 hours. The mixture was diluted with EtOAc and 1N HCl. The layers were separated and the aqueous extracted with EtOAc. The combined EtOAc layers were extracted with 1N HCl, water, then brine. After drying ($NaSO_4$), evaporation *in vacuo* afforded 1.87g (96%) of the 9-[(phenyl)methyl]-5-carbomethoxy-2-(4-trifluoromethylphenyl)-1,2-dihydrocarbazol-4(3H)-one. ^{1}H NMR ($CDCl_3$) δ 7.6 (d, J=8 Hz, 2H), 7.45-7.25 (m, 8H), 6.95 (m, 2H), 5.35 (s, 2H), 4.05

(s, 3H), 3.65 (m, 1H), 3.2 (dd, J=16 and 5 Hz, 1H), 3.0 (dd, J=16 and 10 Hz, 1H), 2.8 (m, 2H). MS (ES) m/e 478.

b) 9-[(Phenyl)methyl]-2-(4-trifluoromethylphenyl)-4-hydroxy-5-carbomethoxy carbazole

A solution of the 9-[(phenyl)methyl]-5-carbomethoxy-2-(4-trifluoromethylphenyl-1,2-dihydrocarbazol-4(3H)-one (1.87 g, 3.92 mM) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.89 g, 3.92 mM) in 39 mL of toluene was refluxed for 25 minutes. The mixture was purified by column chromatography on silica gel (elution with toluene) to afford 1.10 g (59%) of the 9-[(phenyl)methyl]-2-(4-trifluoromethylphenyl)-4-hydroxy-5-carbomethoxy carbazole. ^{1}H NMR ($CDCl_3$) δ 10.65 (s, 1H), 8.05 (d, J=8 Hz, 1H), 7.8 (m, 3H), 7.65 (m, 3H), 7.6 (d, J=8 Hz, 1H), 7.45 (dd, J=8 and 8 Hz, 1H), 7.3-7.1 (m, 2H), 5.6 (s, 2H), 4.1 (s, 3H). MS (ES) m/e 444. 476.

c) 9-[(Phenyl)methyl]-2-(4-trifluoromethylphenyl)-4-hydroxy-5-carbamoyl carbazole

A solution of the 9-[(phenyl)methyl]-2-(4-trifluoromethylphenyl)-4-hydroxy-5-carbomethoxy carbazole (1.10 g, 2.31 mM) in 35 ml THF and 140 mL concentrated aqueous ammonium hydroxide was sonicated for 6 hours at 30-40 °C. The precipitated solid was filtered and washed with water. Trituration with Et_2O, then with 2:1 Et_2O/CH_2Cl_2 afforded 0.20g (19%) of the 9-[(phenyl)methyl]-2-(4-trifluoromethylphenyl)-4-hydroxy-5-carbamoyl carbazole. ^{1}H NMR (DMSO-d6) δ 10.8 (s, 1H), 8.9 (bs, 1H), 8.45 (bs, 1H), 8.0 (d, J=8 Hz, 2H), 7.8 (d, J=8 Hz, 2H), 7.6 (s, 1H), 7.5 (m, 2H), 7.3-7.1 (m, 6H), 7.0 (s, 1H), 5.8 (s, 2H). MS (ES) m/e 444, 461.

d) {9-[(Phenyl)methyl]-2-(4-trifluoromethylphenyl)-5-carbamoylcarbazol-4-yl}oxyacetic acid, methyl ester

60% Sodium hydride in mineral oil (22 mg, 0.54 mM) was added to a solution of the 9-[(phenyl)methyl]-2-(4-trifluoromethylphenyl)-4-hydroxy-5-carbamoyl carbazole (0.20 g, 0.43 mM) in 15 mL DMF and 3 ml THF. After 7 minutes, methyl bromoacetate (56 µl, 0.59 mM) was added and the resultant mixture stirred at room temperature for 1 hour. The mixture was diluted with ethyl acetate and washed with H_2O. The aqueous layer was extracted with ethyl acetate. The combined organic layers were extracted with saturated brine, dried over sodium sulfate, filtered, and concentrated. The residue was purified by column chromatography on silica gel (elution with ethyl acetate) to afford 0.19 g (84%) of the {9-[(phenyl)methyl]-2-(4-trifluoromethylphenyl)-5-carbamoylcarbazol-4-yl}oxyacetic acid, methyl ester. ^{1}H NMR (DMSO-d6) δ 8.0 (d, J=8 Hz, 2H), 7.85 (d, J=8 Hz, 2H), 7.7 (s, 1H), 7.6 (d, J=8 Hz, 1H), 7.6 (bs, 1H), 7.4 (dd, J=8 and 8 Hz, 1H), 7.3-7.1 (m, 6H), 7.1 (d, J=8 Hz, 1H), 7.0 (s, 1H), 5.8 (s, 2H), 5.1 (s, 2H), 3.7 (s, 3H). MS (FD) m/e 516,533.

Elemental Analyses for $C_{30}H_{23}F_3N_2O_4$:.

Calculated: C, 67.66; H, 4.36; N, 5.26.

Found: C, 68.38; H, 4.29 ; N 5.67,.

e) {9-[(Phenyl)methyl]-2-(4-trifluoromethylphenyl)-5-carbamoylcarbazol-4-yl}oxyacetic acid

A solution of the {9-[(phenyl)methyl]-2-(4-trifluoromethylphenyl)-5-carbamoylcarbazol-4-yl}oxyacetic acid, methyl ester (101 mg, 0.19 mM) and 0.95 mL (1.9 mM) of 2 N NaOH in 9.5 mL of ethanol was stirred for 30 minutes at 25 °C. The reaction was acidified with 1N HCl to pH =2. After stirring 30 minutes, the resultant white precipitate was collected by filtration, washed with water, then dried *in vacuo* to afford 73 mg (75%) {9-[(phenyl)methyl]-2-(4-trifluoromethylphenyl)-5-carbamoylcarbazol-4-yl}oxyacetic

acid. ^{1}H NMR (DMSO-d6) δ 11.0 (bs, 1H), 8.0 (d, J=8 Hz, 2H), 7.85 (d, J=8 Hz, 2H), 7.8 (bs, 1H), 7.7 (s, 1H), 7.65 (d, J=8 Hz, 1H), 7.4 (m, 2H), 7.3-7.1 (m, 6H), 7.0 (s, 1H), 5.8 (s, 2H), 5.0 (s, 2H). MS (ES) m/e 502,519.

Elemental Analyses for $C_{29}H_{21}F_3N_2O_4$:

Calculated: C, 67.17; H, 4.09; N, 5.40.

Found: C, 67.05; H, 4.11; N, 5.31.

Example 12

Preparation of 9-benzyl-5-(2-methanesulfonamido)ethyloxy-7-methoxy-1,2,3,4-tetrahydrocarbazole-4-carboxamide

A. Preparation of 5-(2-amino)ethyloxy-9-benzyl-7-methoxy-1,2,3,4-tetrahydrocarbazole-4-carboxamide

To 1.93ml (1.93mmol) 1M lithium aluminum hydride/THF in 13ml THF at 0°C was added H_2SO_4 (53µl, 0.97mmol) dropwise over 5 min. The mixture was allowed to stir at room temperature 1 hour, then a solution of 9-benzyl-7-methoxy-5-cyanomethyloxy-1,2,3,4-tetrahydrocarbazole-4-carboxamide (0.50g, 1.29mmol) in 13ml THF was added dropwise at a rate which kept the temperature below 26°C. After an additional 45 minutes, the reaction was quenched with 0.5ml 1:1 THF/H_2O, 0.75ml 13% NaOH, and finally 80µl H_2O. The reaction was diluted with EtOAc and saturated $NaHCO_3$, and the layers separated. The organic layer was extracted with brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue was chromatographed on silica gel eluting with 9:1:0.1 CH_2Cl_2/MeOH/NH_4OH to give the subtitled product (0.28g, 55%). MS (ES+) 394

B. Preparation of 9-benzyl-5-(2-methanesulfonamido)ethyloxy-7-methoxy-1,2,3,4-tetrahydrocarbazole-4-carboxamide

To 0.20g (0.51mmol) of the product from Part A in 10ml THF at 0°C was added triethylamine (71µl, 0.51mmol) and methanesulfonylchloride (39µl, 0.51mmol). After 40 minutes at 0°C, the reaction was diluted with EtOAc and saturated $NaHCO_3$, and the layers separated. The organic layer was extracted with brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue was chromatographed on silica gel eluting with 20:1 CH_2Cl_2/MeOH and crystallized from EtOAc/hexane to give the titled product (0.13g, 54%). MS (ES+) 472

Elemental Analyses for $C_{24}H_{29}N_3O_5S$:

Calculated:	C 61.13; H 6.20; N 8.91
Found:	C 61.04; H 6.16; N 9.21

Example 13

Preparation of 9-benzyl-4-(2-methanesulfonamido)ethyloxy-2-methoxycarbazole-5-carboxamide

A. Preparation of 4-(2-amino)ethyloxy-9-benzyl-2-methoxycarbazole-5-carboxamide

To 1.25ml (1.25mmol) 1M lithium aluminum hydride/THF in 8.3ml THF at 0°C was added H_2SO_4 (34.5µl, 0.63mmol) dropwise over 5 min. The mixture was allowed to stir at room temperature 1 hour, then a suspension of 9-benzyl-4-cyanomethyloxy-2-methoxycarbazole-5-carboxamide (0.32g, 0.83mmol) in 8.3ml THF was added dropwise at a rate which kept the temperature below 26°C. After an additional 45 minutes, the reaction was quenched with 0.32ml 1:1 THF/H_2O, 0.48ml 13% NaOH, and finally 51µl H_2O. The reaction was

diluted with EtOAc and saturated $NaHCO_3$, and the layers separated. The organic layer was extracted with brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue was chromatographed on silica gel eluting with 9:1:0.1 CH_2Cl_2/MeOH/NH_4OH to give the subtitled product (148mg, 46%). MS (ES+) 390

B. Preparation of 9-benzyl-4-(2-methanesulfonamido)ethyloxy-2-methoxycarbazole-5-carboxamide

To 107mg (0.27mmol) of the product from Part A in 11ml THF at 0°C was added triethylamine (38µl, 0.27mmol) and methanesulfonylchloride (21µl, 0.27mmol). After 40 minutes at 0°C, the reaction was diluted with EtOAc and saturated $NaHCO_3$, and the layers separated. The organic layer was extracted with brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue was chromatographed on silica gel eluting with 10:1 CH_2Cl_2/acetone and crystallized from EtOAc/hexane to give the titled product (28.6mg, 22%). MS (ES+) 468

Elemental Analyses for $C_{24}H_{25}N_3O_5S$:

Calculated: C 61.66; H 5.39; N 8.99

Found: C 61.52; H 5.31; N 8.81

Example 14

Preparation of 9-benzyl-4-(2-trifluoromethanesulfonamido)ethyloxy-2-methoxycarbazole-5-carboxamide

To 31.2mg (0.08mmol) of the product from Example 13, Part A in 3.2ml THF at 0°C was added triethylamine (11.1µl, 0.08mmol) and trifluoromethanesulfonylchloride (8.5µl, 0.08mmol). After 40 min at 0°C, the reaction was

diluted EtOAc and saturated $NaHCO_3$, and the layers separated. The organic layer was extracted with brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue was chromatographed on silica gel eluting with a CH_2Cl_2/EtOAc gradient and triturated with ether to give the titled product (19.3mg, 46%). MS (ES+) 522

Elemental Analyses for $C_{24}H_{22}F_3N_3O_5S$:

Calculated: C 55.27; H 4.25; N 8.06

Found: C 55.11; H 4.40; N 7.99

Example 15

Preparation of 9-benzyl-5-methanesulfonamidoylmethyloxy-7-methoxy-1,2,3,4-tetrahydrocarbazole-4-carboxamide

To 51mg (0.125mmol) of (9-benzyl-4-carbamoyl-7-methoxy-1,2,3,4-tetrahydrocarbazol-5-yl)oxyacetic acid in 25ml THF was added carbonyldiimidazole (20.2mg, 0.125mmol). The reaction was refluxed for 21 hours, then allowed to cool to room temperature . To this was added a mixture of methanesulfonamide (11.9mg, 0.125mmol) and diazabicycloundecene (18.7µl, 0.125mmol) in 2.5ml THF. After 3.5 hours, the reaction was diluted with EtOAc and extracted with 10% $NaHSO_3$, saturated $NaHCO_3$, 10% $NaHSO_3$, and brine, respectively. The organic layer was dried with sodium sulfate and evaporated *in vacuo*. The residue was chromatographed on silica gel eluting with a CH_2Cl_2/EtOH gradient to give the titled product (8mg, 10%).

High Resolution MS for $C_{24}H_{27}N_3O_6S$:

Calculated: 485.1621

Found: 485.1625

Example 16

Preparation of 9-benzyl-4-methanesulfonamidoylmethyloxy-carbazole-5-carboxamide

To 48mg (0.13mmol) of (9-benzyl-5-carbamoyl-carbazol-4-yl)oxyacetic acid in 26ml THF was added carbonyldiimidazole (21mg, 0.13mmol). The reaction was refluxed for 25 hours, then allowed to cool to room temperature . To this was added a mixture of methanesulfonamide (12mg, 0.13mmol) and diazabicycloundecene (19µl, 0.13mmol) in 2.6ml THF. After 3 hours, the reaction was diluted with EtOAc and extracted with 10% $NaHSO_3$, then brine. The organic layer was dried with sodium sulfate and evaporated *in vacuo*. The residue was chromatographed on silica gel eluting with a CH_2Cl_2/EtOH gradient to give impure product. Extraction from EtOAc into saturated $NaHCO_3$ and reacidification gave the titled product (3.9mg, 6.7%).

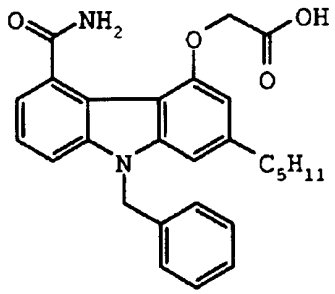
High Resolution MS for $C_{23}H_{21}N_3O_5S$:

Calculated: 452.1280

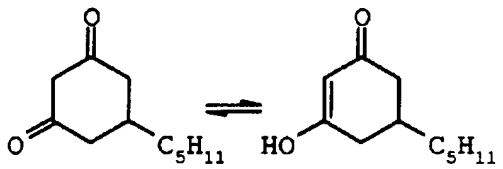
Found: 452.1284

Example 17

[5-carbamoyl-2-pentyl-9-(phenylmethyl)carbazol-4-yl]oxyacetic acid



A. Preparation of a mixture of 5-pentylcyclohexa-1,3-dione and its enol isomer

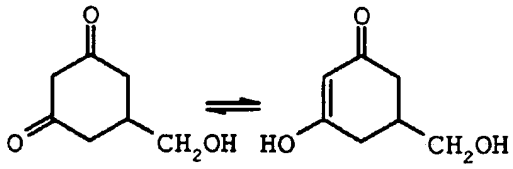


Sodium hydroxide (1.98 g, 49.5 mmol) was added to a stirred suspension of olivetol (7.20 g, 39.9 mmol) in THF (20 mL)/H_2O (20 mL) at ambient temperature under nitrogen atmosphere. The solution was stirred until it became a clear solution. Stir bar was removed before 5% Rh/Al_2O_3 (500 mg) was added to the solution. The mixture was then subject to hydrogenation condition under a 60 pounds per square inch hydrogen atmosphere in a Parr shaker for 17 hours. After filtration through celite, the filtrate was cooled to 0 °C, then treated with 5 N HCl (10.9 mL). The mixture was evaporated *in vacuo* at 40 °C and the residue was chromatographed on silica (gradient 40-100% ethyl acetate in hexane, then 0-15% methanol in ethyl acetate) to give sub-titled compound (4.80 g, 66%) as a white solid mixture of keto/enol isomers in a 3:2 ratio. mp 68.5-69.5 °C; IR (KBr) 3200-2400 (br), 1610, 1542 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (br t, J = 6.6 Hz, 3H, $-CH_3$), 3.38 (s, 2H, $-CH_2-$ of keto isomer), 4.13 (s, 1H, =CH- of enol isomer), 8.90 (br s, 1H, -OH); ESIMS *m/e* 183 (M^++1);

Elemental Analyses for $C_{11}H_{18}O_2$:

Calculated:	C, 72.49; H, 9.95.
Found:	C, 72.72; H, 9.95.

B. Preparation of a mixture of 5-(hydroxymethyl)clohexa-1,3-dione and its enol isomer



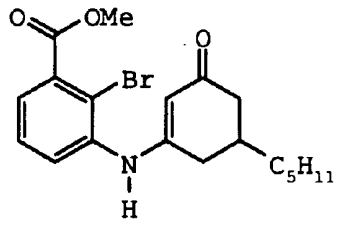
Following the experimental procedure as described in part A, above synthesis of subtitled compound was obtained in a 75% yield. IR (KBr) 3547, 3453 (br), 1633, 1580 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.90-2.30 (m, 5H), 3.30 (br s, 2H, $-CH_2O-$), 4.61 (br s, 1H, -OH), 5.13 (s, 1H), 10.94 (s, 1H, -OH); ESIMS *m/e* 143 (M^++1);

Elemental Analyses for $C_7H_{10}O_3$:

Calculated: C, 59.14; H, 7.09.

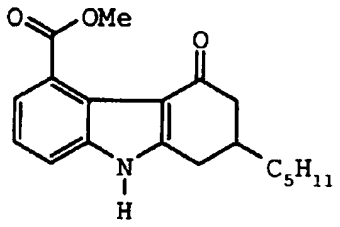
Found: C, 59.44; H, 7.08.

C. Preparation of 3-(2-bromo-3-carbomethoxyanilino)-5-pentylcyclohex-2-en-1-one



A stirred mixture of methyl-3-amino-2-bromobenzoate prepared as described in Preparation 4 (5.12 g, 22.3 mmol) and the compound of Part A (4.06 g, 22.3 mmol) was heated in an oil bath at 150 °C for 1.4 hours under a positive nitrogen pressure to continuously remove the water vapor. At ambient temperature, the mixture was chromatographed on silica (gradient 30-100% ethyl acetate in hexane) to provide subtitled compound (6.06 g, 69%) as a white solid. mp 132.0-134.0 °C; IR (KBr) 3220 (br), 1726, 1580 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (br t, *J* = 6.6 Hz, 3H, $-CH_3$), 1.25-1.45 (m, 8H), 2.05-2.27 (m, 2H), 2.35-2.57 (m, 3H), 3.94 (s, 3H, $-OCH_3$), 5.57 (s, 1H, =CH-), 6.44 (br s, 1H, -NH), 7.35 (t, *J* = 6.8 Hz, 1H), 7.53 (d, *J* = 6.8 Hz, 2H); ESIMS *m/e* 394 (M^++1, ^{79}Br), 396(M^++1, ^{81}Br).

D. Preparation of 5-carbomethoxy-1,2-dihydro-2-pentyl-9H-carbazol-4(3H)-one



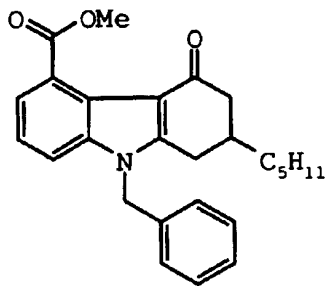
Triethylamine (2.09 mL, 15.0 mmol) was added to a stirred suspension of the compound of part C, above (3.94 g, 10.0 mmol), $Pd(OAc)_2$ (338 mg, 1.50 mmol), and tri-*o*-tolylphosphine (914 mg, 3.00 mmol) in acetonitrile (40 mL) at ambient temperature under nitrogen atmosphere. The resultant mixture was then heated in an oil bath at 85 °C for 1 h. The mixture was evaporated *in vacuo* at 35 °C and the residue was chromatographed on silica (gradient 20-100% ethyl acetate in hexane) to give subtitled compound (2.45 g, 78%) as a white solid. mp 116.0-117.5 °C; IR (KBr) 3379 (br), 3180 (Br), 1725, 1627 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89 (br t, J = 6.6 Hz, 3H, $-CH_3$), 1.20-1.47 (m, 8H), 2.20-2.32 (m, 2H), 2.50-2.67 (m, 2H), 2.92-3.05 (m, 1H), 4.02 (s, 3H, $-OCH_3$), 7.18-7.26 (m, 1H), 7.35-7.43 (m, 2H), 9.20-9.42 (br s, 1H, -NH); ESIMS *m/e* 314 (M^++1);

Elemental Analyses for $C_{19}H_{23}NO_3$:

Calculated: C, 72.82; H, 7.40; N, 4.47.

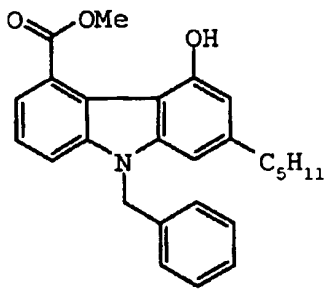
Found: C, 72.59; H, 7.43; N, 4.51.

E. Preparation of 5-carbomethoxy-1,2-dihydro-2-pentyl-9-(phenylmethyl)carbazol-4(3H)-one



Benzylbromide (1.25 mL, 10.5 mmol) was added to a stirred suspension of the compound of example 17D (3.00 g, 9.57 mmol) and potassium carbonate (1.98 g, 14.4 mmol) in anhydrous DMF (30 mL) under nitrogen atmosphere. The resultant mixture was stirred for 5 hours. The mixture was evaporated *in vacuo* at 40 °C and the residue was chromatographed on silica (gradient 10-60% ethyl acetate in hexane) to give subtitled compound (3.28 g, 85%) as a white solid. mp 119.0-120.5 °C; IR (KBr) 1723, 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87 (br t, J = 6.6 Hz, 3H, $-CH_3$), 1.23-1.52 (m, 8H), 2.25-2.40 (m, 2H), 2.47-2.57 (m, 1H), 2.69 (d, J = 12.8 Hz, 1H), 2.99 (dd, J = 16.6, 3.6 Hz, 1H), 4.05 (s, 3H, $-OCH_3$), 5.36 (s, 2H), 6.98-7.02 (m, 2H), 7.20-7.40 (m, 6H); ESIMS *m/e* 404 (M^++1).

F. Preparation of 5-carbomethoxy-4-hydroxy-2-pentyl-9-(phenylmethyl)carbazole



(a) from DDQ oxidation: DDQ (563 mg, 2.48 mmol) was added to a stirred suspension of the compound of part E, above (1.00 g, 2.48 mmol) in anhydrous toluene (30 mL) under nitrogen atmosphere. The resultant mixture was heated to reflux for 25 min. At ambient temperature, the mixture was subject to chromatographic purification on silica (gradient 0-30% ethyl acetate in toluene) to give subtitled compound (290 mg, 29%) as a yellow solid (310 mg, 31%).

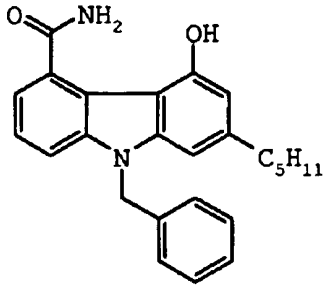
(b) from benzenesulfinate elimination: Sodium hydride (60% in oil, 192 mg, 4.80 mmol) was added to a stirred solution of the compound of part E, above (807 mg, 2.00 mmol) and methyl benzenesulfinate (375 mg, 2.40 mmol) in anhydrous 1,4-dioxane (10 mL) under nitrogen atmosphere. The mixture was heated in an oil bath at 50 °C for 2h 15 min. After dilution with additional 15 mL 1,4-dioxane, the mixture was treated with acetic acid (0.343 mL, 6.00 mmol) and the resultant suspension was heated to reflux for 40 min. The mixture was evaporated *in vacuo* and the residue was chromatographed on silica (gradient 0-5% ethyl acetate in toluene) to afford subtitled compund (690 mg, 86%) as a yellow solid. mp 130.0-132.0 °C; IR (KBr) 3200 (br), 1686 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87 (br t, J = 6.6 Hz, 3H, $-CH_3$), 1.25-1.38 (m, 4H), 1.60-1.75 (m, 2H), 2.69 (t, J = 7.7 Hz, 2H), 4.10 (s, 3H, $-OCH_3$), 5.52 (s, 2H), 6.71 (s, 1H), 6.76 (s, 1H), 7.09-7.11 (m, 2H), 7.20-7.30 (m, 3H), 7.37 (t, J = 8.0 Hz, 1H), 7.55 (d, J = 8.0 Hz, 1H), 7.97 (d, J = 8.0 Hz, 1H), 10.43 (s, 1H, -OH); ESIMS *m/e* 402 (M^++1);

Elemental Analyses for $C_{26}H_{27}NO_3 \cdot 0.2(C_7H_8)$:

Calculated: C, 78.37; H, 6.86; N, 3.34.

Found: C, 78.48; H, 6.68; N, 3.53.

G. Preparation of 5-carbamoyl-4-hydroxy-2-pentyl-9-(phenylmethyl)carbazole



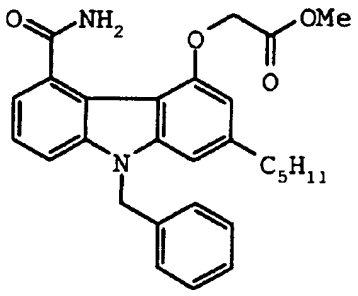
Ammonia was bubbled through a stirred suspension of the compund of part F, above (590 mg, 1.47 mmol) in ammonia water (50 mL)/THF (10 mL) at -25 °C for 5 minutes in a pressure bottle. The bottle was screw-capped before the mixture was allowed to stir at ambient temperature for 3 days. After cooling to -25 °C, the screw cap was removed and the mixture was allowed to stir at ambient temperature for 10 minutes. After concentration, the residue was subject to chromatographic purification on silica (gradient 0-40% tetrahydrofuran in toluene) to recover the compound of part F (160 mg, 27%) and obtain the desired subtitled product (397 mg, 70%) as a yellowish solid. IR (KBr) 3437, 3200 (br), 1633, 1601 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 (br t, J = 6.6 Hz, 3H, $-CH_3$), 1.22-1.38 (m, 4H), 1.60-1.75 (m, 2H), 2.69 (t, J = 7.7 Hz, 2H), 5.52 (s, 2H), 6.16 (s, 1H, -NH), 6.53 (s, 1H, -NH), 6.72 (s, 1H), 6.76 (s, 1H), 7.07-7.11 (m, 2H), 7.23-7.30 (m, 3H), 7.35 (t, J = 7.7 Hz, 1H), 7.43 (d, J = 7.7 Hz, 1H), 7.48 (d, J = 7.7 Hz, 1H), 9.80 (s, 1H, -OH); ESIMS m/e 387 (M^++1);

Elemental Analyses for $C_{25}H_{26}N_2O_2$:

Calculated: C, 77.69; H, 6.78; N, 7.25.

Found: C, 77.69; H, 6.63; N, 7.15.

H. Preparation of [5-carbamoyl-2-pentyl-9-(phenylmethyl)carbazol-4-yl]oxyacetic acid, methyl ester



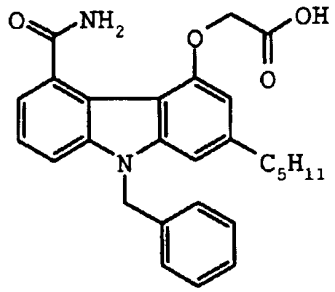
Methyl bromoacetate (48.0 mg, 0.314 mmol) was added to a stirred suspension of the compound of example 17G, above (110 mg, 0.285 mmol) and cesium carbonate (186 mg, 0.570 mmol) in anhydrous DMF (2 mL) at ambient temperature under nitrogen atmosphere. The resultant mixture was stirred for 1 hour. After concentration *in vacuo* at 40 °C, the residue was chromatographed on silica (gradient 10-60% tetrahydrofuran in toluene) to give subtitled product (115 mg, 88%) as a white solid. mp 195.0-196.0 °C; IR (KBr) 3365 (br), 3157 (br), 1758, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87 (br t, J = 6.6 Hz, 3H, $-CH_3$), 1.22-1.35 (m, 4H), 1.58-1.70 (m, 2H), 2.69 (t, J = 7.6 Hz, 2H), 3.84 (s, 3H, $-OCH_3$), 4.89 (s, 2H, $-OCH_2-$), 5.50 (s, 2H, $-NCH_2-$), 5.95 (br s, 1H, -NH), 6.08 (br s, 1H, -NH), 6.41 (s, 1H), 6.85 (s, 1H), 7.07-7.11 (m, 2H), 7.23-7.40 (m, 6H); ESIMS *m/e* 459 (M^++1);

Elemental Analyses for $C_{28}H_{30}N_2O_4$:

Calculated: C, 73.34; H, 6.59; N, 6.11.

Found: C, 73.56; H, 6.43; N, 6.25.

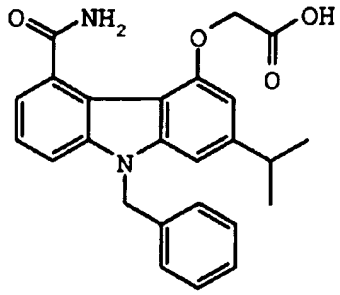
I. Preparation of [5-carbamoyl-2-pentyl-9-(phenylmethyl)carbazol-4-yl]oxyacetic acid



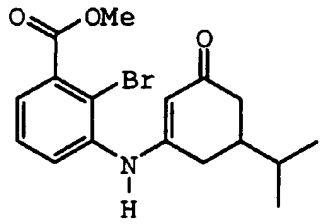
Lithium hydroxide (4.17 N, 86.3 *m*L, 0.360 mmol) was added to a stirred suspension of the compound of Example 17H, above (110 mg, 0.240 mmol) in THF (2 mL)/CH_3OH (0.3 mL)/H_2O (0.3 mL). The resultant mixture was stirred in an oil bath at 55 °C for 30 minutes to form a white suspension. Five milliliter of THF was added to the suspension before it was treated with 5 N HCl (96.0 *m*L, 0.480 mmol) to become a clear solution. After concentration, the white solid was resuspended in THF (0.5 mL)/H_2O (5 mL), sonicated, filtered, and dried to give the subtitled compound (106 mg, 99%) as a white solid. IR (KBr) 3458 (br), 3500-3100 (br), 1656, 1620 cm^{-1}; ^1H NMR (DMSO-d_6) δ 0.80 (br t, *J* = 6.6 Hz, 3H, $-CH_3$), 1.18-1.30 (m, 4H), 1.50-1.62 (m, 2H), 2.61 (br t, *J* = 7.3 Hz, 2H), 4.55 (s, 2H, $-OCH_2-$), 5.60 (s, 2H, $-NCH_2-$), 6.40 (s, 1H), 6.95-7.32 (m, 9H), 7.51 (d, *J* = 8.0 Hz, 1H), 7.70 (br s, 1H, -NH); ESIMS *m/e* 445 (M^++1).

Example 18

[5-carbamoyl-2-(1-methylethyl)-9-(phenylmethyl)carbazol-4-yl]oxyacetic acid

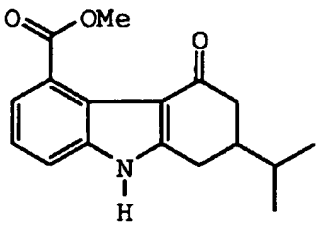


A. Preparation of 3-(2-bromo-3-carbomethoxyanilino)-5-[(1-methyl)ethyl]cyclohex-2-en-1-one



Prepared in 70% yield by the method of Example 17 part C. mp 129.0-130.0 °C; ^{1}H NMR ($CDCl_3$) δ 0.98 (t, J=5.5 Hz, 6H), 1.66 (m, 1H), 2.00 (m, 1H), 2.14 (t, J = 14.8 Hz, 1H), 2.46 (m, 3H), 4.00 (s, 3H), 5.57 (s, 1H), 6.40 (br s, 1H), 7.35 (t, J = 7.9 Hz, 1H), 7.35 (d, J = 7.8 Hz, 2H); ESIMS m/e 366 (M^++1, ^{79}Br), 368 (M^++1, ^{81}Br).

B Preparation of 5-carbomethoxy-1,2-dihydro-2-(1-methylethyl)-9H-carbazol-4(3H)-one



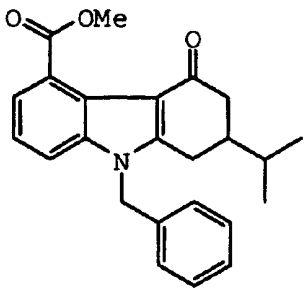
Prepared in 65% yield by the procedure of Example 17D. mp 175.0-177.0 °C; ^{1}H NMR ($CDCl_3$) δ 0.95 (t, *J*=6.7 Hz, 6H), 1.62 (m, 1H), 2.05 (m, 1H), 2.27 (dd, *J* = 16.1, 12.6 Hz, 1H), 2.60 (m, 2H), 2.89 (dd, *J* = 16.4, 4.3 Hz, 1H), 4.02 (s, 3H), 7.23 (m, 1H), 7.36 (m, 2H), 9.28 (br s, 1H); ESIMS *m/e* 286 (M^++1);

Elemental Analyses for $C_{17}H_{19}NO_3$:

Calculated: C,71.56; H,6.71; N,4.91.

Found: C, 71.43; H, 6.62; N, 4.74.

C. Preparation of 5-carbomethoxy-1,2-dihydro-2-(1-methylethyl)-9-(phenylmethyl)carbazol-4(3H)-one



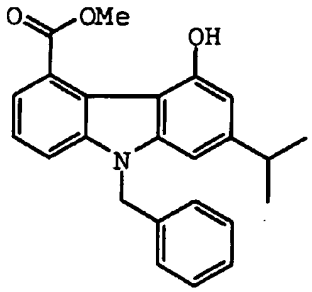
Prepared in 37% yield by the method of Example 17E. mp: 155.0-156.0 °C; ^{1}H NMR ($CDCl_3$) δ 1.28 (d, *J* = 8.0 Hz, 6H), 3.00 (m, 1H), 4.10 (s, 3H), 5.23 (s, 2H), 6.78 (d, *J* = 9.5 Hz, 2H), 7.11 (m, 2H), 7.28 (m, 3H), 7.37 (t, *J* = 7.9 Hz, 1H), 7.54 (d, *J* = 7.9 Hz, 1H), 7.98 (d, *J* = 7.9 Hz, 1H), 10.46 (s, 1H); ESIMS *m/e* 374 (M^++1);

Elemental Analyses for $C_{24}H_{23}NO_3$:

Calculated: C, 77.19; H, 6.21; N, 3.75.

Found: C, 76.96; H, 6.33; N, 3.77.

D. Preparation of 5-carbomethoxy-4-hydroxy-2-(1-methylethyl)-9-(phenylmethyl)carbazole



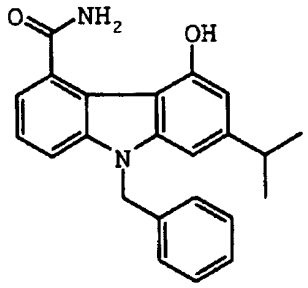
DDQ (1.15 g, 5.07 mmol) was added to a stirred suspension of the compound of Example 18C (1.90 g, 5.07 mmol) in anhydrous toluene (30 mL) under argon atmosphere. The resultant mixture was heated under reflux for 25 min. After cooling to room temperature, the mixture was subjected to chromatography on silica gel eluting with a gradient of hexanes/toluene(1:1) to toluene/EtOAc (97:3). The desired product was obtained a mixture with the corresponding isopropylidene compound. The mixture was dissolved in EtOAc (30 mL) under nitrogen atmosphere, and 0.1 g of PtO_2 was added. The mixture was stirred at room temperature under hydrogen at balloon pressure for 25 min. Filtration through celite, followed by recrystallization from Et_2O/hexanes gave the subtitled compound as a pale yellow crystalline solid (0.705 g; 37% yield). mp: 155.0-156.0 °C; ^1H NMR ($CDCl_3$) δ 1.28 (d, J = 8.0 Hz, 6H), 3.00 (m, 1H), 4.10 (s, 3H), 5.23 (s, 2H), 6.78 (d, J = 9.5 Hz, 2H), 7.11 (m, 2H), 7.28 (m, 3H), 7.37 (t, J = 7.9 Hz, 1H), 7.54 (d, J = 8.0 Hz, 1H), 7.98 (d, J = 7.9 Hz, 1H), 10.46 (s, 1H); ESIMS *m/e* 374 (M^++1);

Elemental Analyses for $C_{24}H_{23}NO_3$:

Calculated: C, 77.19; H, 6.21; N, 3.75.

Found: C, 76.96; H, 6.33; N, 3.77.

E. Preparation of 5-carbamoyl-4-hydroxy-2-(1-methylethyl)-9-(phenylmethyl)carbazole



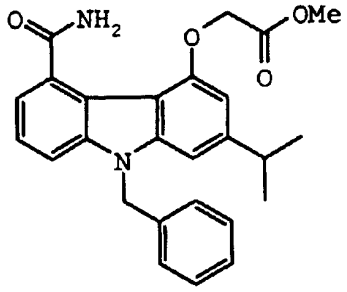
Prepared in 50% yield by the procedure of example 17G. mp 216.0-218.0 °C; ^{1}H NMR ($CDCl_3$) δ 1.29 (d, J = 6.9, 6H), 3.00 (m, 1H), 5.53(s, 2H), 6.16 (br s, 1H), 6.52 (br s, 1H), 6.78 (d, J = 8.6 Hz, 2H), 7.11 (m, 2H), 7.28 (m, 3H), 7.32 (m, 1H), 7.4 (m, 2H), 9.8 (br s, 1H); ESIMS *m/e* 359.3 (M^++1);

Elemental Analyses for $C_{23}H_{22}N_2O_2$:

Calculated: C, 77.07; H, 6.19; N, 7.82.

Found: C, 77.10; H, 6.35; N, 7.74.

F. Preparation of [5-carbamoyl-2-(1-methylethyl)-9-(phenylmethyl)carbazol-4-yl]oxyacetic acid, methyl ester



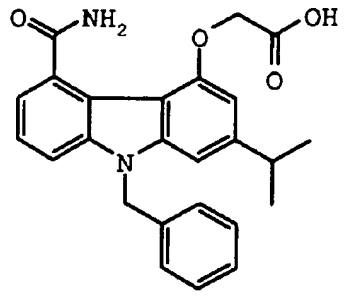
Prepared by the procedure of example 17H in 54% yield. mp 189.0-191.0 °C; ^{1}H NMR ($CDCl_3$) δ 1.27 (d, J = 6.9 Hz, 6H), 2.98 (m, 1H), 3.84 (s, 3H), 4.90 (s, 2H), 5.51(s, 2H), 5.8-6.2 (m, 2H), 6.47 (s, 1H), 6.90 (s, 1H), 7.11 (m, 2H), 7.2-7.4 (m, 6H); ESIMS *m/e* 431 (M^++1);

Elemental Analyses for $C_{26}H_{26}N_2O_4$:

Calculated: C, 72.54; H, 6.09; N, 6.51.

Found: C, 72.58; H, 6.24; N, 6.43.

G. Preparation of [5-carbamoyl-2-(1-methylethyl)-9-(phenylmethyl)carbazol-4-yl]oxyacetic acid



Prepared by the procedure of example Example 17I in 82% yield. ^{1}H NMR ($CDCl_3$) δ 1.20 (d, J = 6.7, 6H), 2.94 (m, 1H), 4.79 (s, 2H), 5.63 (s, 2H), 6.49(s, 1H), 7.00-7.40 (m, 9H), 7.51 (m, 1H), 7.70 (br s, 1H), 12.94 (br s, 1H); ESIMS *m/e* 417 (M^++1);

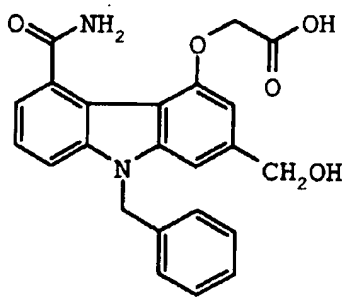
Elemental Analyses for $C_{25}H_{24}N_2O_4$:

Calculated: C, 72.10; H, 5.81; N, 6.73.

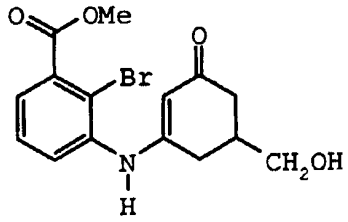
Found: C, 72.11; H, 5.62; N, 6.49.

Example 19

[5-carbamoyl-9-(phenylmethyl)-2-[(tri(-1-methylethyl)silyl)oxymethyl]carbazol-4-yl]oxyacetic acid



A. Preparation of 3-(2-bromo-3-carbomethoxyanilino)-5-(hydroxymethyl)cyclohex-2-en-1-one

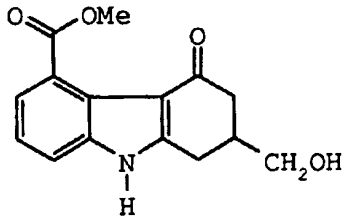


Following the experimental procedure as described in the synthesis of Example 17 part C, subtitled compound was obtained as a white solid in a 68% yield. IR (KBr) 3407 (br), 3364 (br), 3222 (br), 1738, 1600, 1566 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.94 (dd, J = 16.5, 12.5 Hz, 1H), 2.02-2.15 (m, 2H), 2.32 (dd, J = 16.5, 9.9 Hz, 1H), 2.50-2.58 (m, 1H), 3.27-3.42 (m, 2H), 3.83 (s, 3H, $-OCH_3$), 4.55 (s, 1H, =CH-), 4.64 (t, J = 5.1 Hz, 1H, -OH), 7.42-7.58 (m, 3H), 8.76 (s, 1H, -NH); ESIMS m/e 354 (M^++1, ^{79}Br), 356(M^++1, ^{81}Br); Elemental Analyses for $C_{15}H_{16}BrNO_4$:

Calculated: C, 50.87; H, 4.55; N, 3.95.

Found: C, 51.07; H, 4.60; N, 3.93.

B. Preparation of 5-carbomethoxy-1,2-dihydro-2-(hydroxymethyl)-9H-carbazol-4(3H)-one



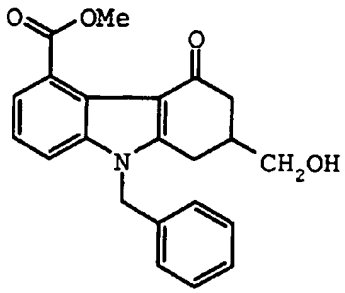
Following the experimental procedure as described in the synthesis of Example 17D, subtitled compound was obtained as a white solid in a 66% yield. IR (KBr) 3350 (br), 1720, 1624 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.92-2.20 (m, 2H), 2.33 (dd, J = 16.0, 3.0 Hz, 1H), 2.44 (dd, J = 16.8, 9.9 Hz, 1H), 2.67 (dd, J = 16.8, 4.0 Hz, 1H), 3.33-3.48 (m, 2H),

4.05 (s, 3H, $-OCH_3$), 7.20-7.26 (m, 1H), 7.33 (d, J = 7.3 Hz, 1H), 7.43 (d, J = 7.9 Hz, 1H), 10.25 (s, 1H, -NH); ESIMS m/e 274 (M^++1);

Elemental Analyses for $C_{15}H_{15}NO_4$:

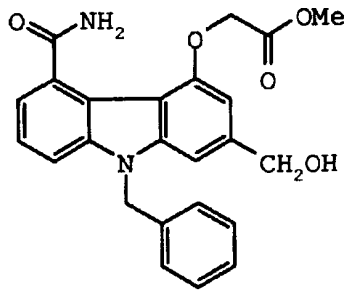
Calculated:	C, 65.93;	H, 5.53; N, 5.13.
Found:	C, 65.68;	H, 5.78; N, 5.08.

C. Preparation of 5-carbomethoxy-1,2-dihydro-2-(hydroxymethyl)-9-(phenylmethyl)carbazol-4(3H)-one



Following the experimental procedure as described in the synthesis of Example 17E, the subtitled compound was obtained as a white solid in a 88% yield. IR (KBr) 3366 (br), 1728, 1632 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.98 (s, 1H, -OH), 2.30-2.62 (m, 3H), 2.72 (dd, J = 16.8, 9.7 Hz, 1H), 3.06 (dd, J = 17.0, 3.6 Hz, 1H), 3.58-3.75 (m, 2H), 4.04 (s, 3H, $-OCH_3$), 5.25-5.40 (m, 2H, $-NCH_2-$), 6.98-7.05 (m, 2H), 7.20-7.40 (m, 6H); ESIMS m/e 364 (M^++1).

D. Preparation of [5-carbamoyl-9-(phenylmethyl)-2-[(tri(-1-methylethyl)silyl)oxymethyl]carbazol-4-yl]oxyacetic acid, methyl ester



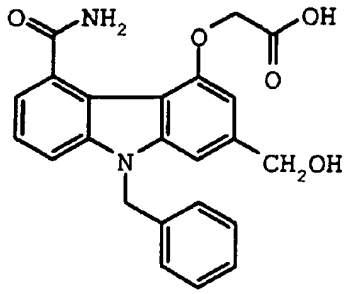
etrabutylammonium fluoride (1 N in THF, 0.626 mL) was added to a stirred solution of the compound of Example 23D (300 mg, 0.522 mmol) in THF (5 mL). The mixture was stirred at ambient temperature for 1 hour. After conentration *in vacuo* at 35 °C, the residue was subject to chromatographic purification (gradient 50-100% tetrahydrofuran in toluene, then 5% methanol in tetrahydrofuran) to give subtitled compound (122 mg, 56%) as a white solid. IR (KBr) 3380 (br), 3205 (br), 1733, 1641, 1628 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.69 (s, 3H, $-OCH_3$), 4.55 (s, 2H, $-OCH_2-$), 4.86 (s, 2H, $-OCH_2-$), 5.22 (br s, 1H, -OH), 5.62 (s, 2H, $-NCH_2-$), 6.53 (s, 1H), 7.00-7.25 (m, 8H), 7.32 (br t, J = 7.7 Hz, 1H), 7.50 (br d, J = 7.7 Hz, 1H), 7.53 (br d, J = 7.7 Hz, 1H); ESIMS *m/e* 419 (M^++1);

Elemental Analyses for $C_{24}H_{22}N_2O_5$:

Calculated: C, 68.89; H, 5.30; N, 6.69.

Found: C, 68.80; H, 5.17; N, 6.72.

E. Preparation of [5-carbamoyl-9-(phenylmethyl)-2-[(tri(-1-methylethyl)silyl)oxymethyl]carbazol-4-yl]oxyacetic acid



Following the experimental procedure as described in the synthesis of Example 17I, subtitled compound was obtained as a white solid in a 99% yield. IR (KBr) 3427, 3331 (br), 1732, 1682, 1636 cm^{-1}; ^1H NMR (DMSO-d_6) δ 4.55 (d, J = 4.6 Hz, 2H, $-OC\underline{H}_2OH$), 4.78 (s, 2H, $-OCH_2-$), 5.25 (br t, J = 4.6 Hz, 1H, -OH), 5.62 (s, 2H, $-NCH_2-$), 6.57 (s, 1H), 7.00-7.25 (m, 7H), 7.33 (br t, J = 7.8 Hz, 1H), 7.39 (s, 1H, -NH), 7.55 (d, J = 7.8 Hz, 1H), 7.72 (s, 1H, -NH), 12.93 (s, 1H, $-CO_2H$); ESIMS m/e 405 (M^++1);

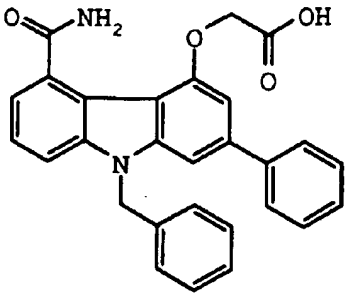
Elemental Analyses for $C_{23}H_{20}N_2O_5 \bullet 0.3H_2O$:

Calculated: C, 67.41; H, 5.07; N, 6.84.

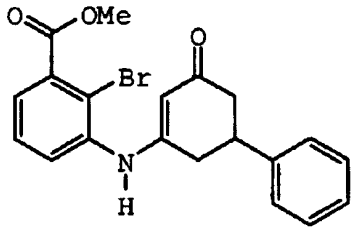
Found: C, 67.34; H, 5.13; N, 6.98.

Example 20

Preparation of [5-carbamoyl-2-phenyl-9-(phenylmethyl)carbazol-4-yl]oxyacetic acid



A. Preparation of 3-(2-bromo-3-carbomethoxyanilino)-5-phenylcyclohex-2-en-1-one



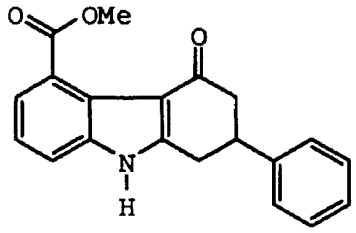
Prepared in 61% yield by the method of Example 17, part A. IR (KBr) 3180 (br), 1734, 1592 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.64-2.71 (m, 2H), 2.84 (dd, J = 11.7, 16.2 Hz, 1H), 3.45-3.49 (m, 1H), 3.95 (s, 3H) 5.67 (s, 1H), 6.29 (br s, 1H), 7.29-7.40 (m, 6H), 7.54-7.59 (m, 2H); ESIMS m/e 400 (M^++1, ^{79}Br), 402 (M^++1, ^{81}Br);

Elemental Analyses for $C_{20}H_{18}BrNO_3$:

Calculated: C, 60.01; H, 4.53; N, 3.50.

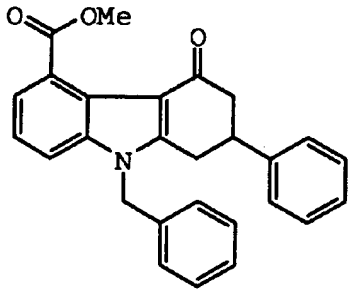
Found: C, 60.23; H, 4.80; N, 3.47.

B. Preparation of 5-carbomethoxy-1,2-dihydro-2-phenyl-9H-carbazol-4(3H)-one



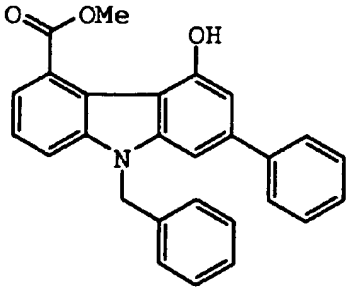
Prepared by the method of Example 17D in 70% yield. IR (KBr) 3180, 1736, 1628 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.70 (d, J = 4 Hz, 1H), 2.72 (s, 1H), 2.97-3.03 (m, 2H), 4.03 (s, 3H), 7.18-7.39 (m, 8H), 9.52 (br s, 1H); ESIMS m/e 320 (M^++1).

C. Preparation of 5-carbomethoxy-1,2-dihydro-2-phenyl-9-(phenylmethyl)carbazol-4(3H)-one



Prepared in 85% yield by the method of Example 17E. IR (KBr) 1723, 1652 cm^{-1}; ESIMS *m/e* 410 (M^++1).

D. Preparation of 5-carbomethoxy-4-hydroxy-2-phenyl-9-(phenylmethyl)carbazole



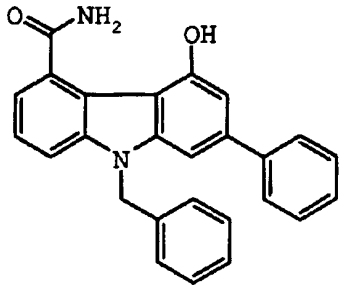
Prepared in 50% yield by the method (a) of Example 17F. IR (KBr) 3326, 1711 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.10 (s, 3H), 5.52 (s, 2H), 7.08-7.10 (m, 4H), 7.24-7.56 (m, 7H), 7.38 (d, *J* = 8.1 Hz, 1H), 7.55 (d, *J* = 8.0 Hz, 2H), 7.97 (d, *J* = 8.1 Hz, 1H) 10.43 (br s, 1H); ESIMS *m/e* 408 (M^++1);

Elemental Analyses for $C_{27}H_{21}NO_3 \bullet 0.1\ C_7H_8$:

Calculated: C, 79.85; H, 5.27; N, 3.36.

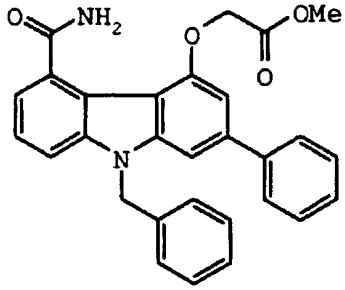
Found: C, 80.19; H, 5.32; N, 3.49.

E. Preparation of 5-carbamoyl-4-hydroxy-2-phenyl-9-(phenylmethyl)carbazole



Prepared in 40% yield by the method of Example 17G. ^{1}H NMR ($CDCl_3$) δ 5.58 (s, 2H), 6.25 (s, 1H), 6.59 (s, 1H), 7.11-7.16 (m, 4H), 7.26-7.48 (m, 8H), 7.52 (d, *J* = 8.1 Hz, 1H), 7.68 (d, *J* = 7.2 Hz, 2H), 9.99 (br s, 1H); ESIMS *m/e* 393 (M^++1).

F. Preparation of [5-carbamoyl-2-phenyl-9-(phenylmethyl)carbazol-4-yl]oxyacetic acid, methyl ester



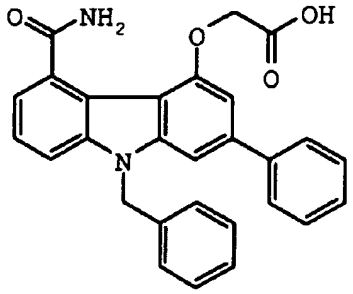
Prepared in 58% yield by the method of Example 17H. IR (KBr) 3359, 1755, 1634 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.85 (s, 3H), 4.96 (s, 2H), 5.58 (s, 2H), 5.92 (br s, 2H), 7.11 (s, 1H), 7.13-7.24 (m, 2H), 7.26-7.30 (m, 3H), 7.34-7.47 (m, 7H), 7.59 (d, *J* = 7.3 Hz, 2H); ESIMS *m/e* 465 (M^++1);

Elemental Analyses for $C_{29}H_{24}N_2O_4$:

Calculated: C, 74.98; H, 5.21; N, 6.03.

Found: C, 74.97; H, 5.22; N, 5.80.

G. Preparation of [5-carbamoyl-2-phenyl-9-(phenylmethyl)carbazol-4-yl]oxyacetic acid



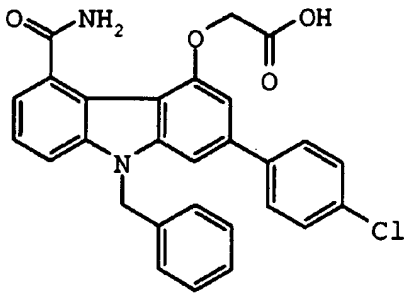
Prepared in 86% yield by the method of Example 17I. IR (KBr) 3426, 3332, 2625-2100 (br),1734, 1636 cm^{-1}; ^1H NMR (DMSO-d_6) δ 4.94 (s, 2H), 5.57 (s, 2H),6.96 (s, 1H), 7.06-7.31 (m, 6H), 7.33-7.47 (m, 5H), 7.55-7.60 (m, 2H), 7.71-7.73 (m, 3H), 12.94 (br s, 1H); ESIMS *m/e* 451 (M^++1); Elemental Analyses for $C_{28}H_{22}N_2O_4$:

Calculated: C, 74.65; H, 4.92; N, 6.22.

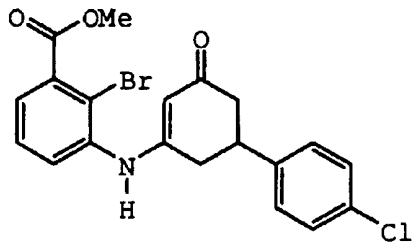
Found: C, 74.87; H, 5.15; N, 6.11.

Example 21

[5-carbamoyl-2-(4-chlorophenyl)-9-(phenylmethyl)carbazol-4-yl]oxyacetic acid



A. Preparation of 3-(2-bromo-3-carbomethoxyanilino)-5-(4-chlorophenyl)cyclohex-2-en-1-one



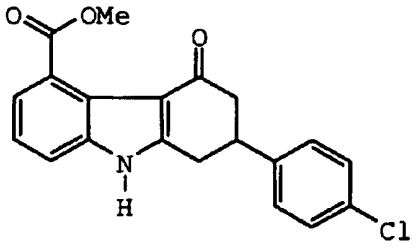
Prepared by the method of Example 17, part C in 80% yield. ^{1}H NMR ($CDCl_3$) δ 2.66 (m, 3H), 2.86 (m, 1H), 3.44 (m, 1H), 3.95 (s, 3H), 5.75 (s, 1H), 7.24 (m, 3H), 7.32 (m, 3H), 7.57 (t, *J* = 7.1 Hz, 2H); ESIMS *m/e* 434 (M^++1, $^{79}Br^{35}Cl$), 436 (M^++1, $^{81}Br^{35}Cl$, $^{79}Br^{37}Cl$), 438 (M^++1, $^{81}Br^{37}Cl$);

Elemental Analyses for $C_{20}H_{17}BrClNO_3$:

Calculated: C, 55.26; H, 3.94; N, 3.22.

Found: C, 55.55; H, 3.91; N, 3.21.

B. Preparation of 5-carbomethoxy-1,2-dihydro-2-(4-chlorophenyl)-9H-carbazol-4(3H)-one



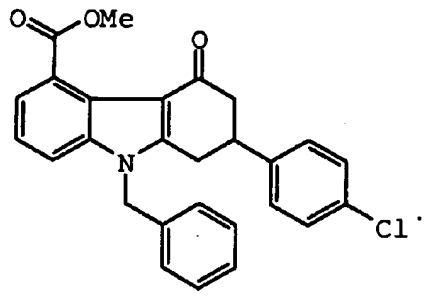
Prepared by the method of Example 17D in 64% yield. ^{1}H NMR ($CDCl_3$) δ 2.72 (m, 2H), 2.99 (dd, *J* = 16.7, 16.5 Hz, 1H), 3.12 (dd, *J* = 16.7, 4.7 Hz, 1H), 3.45 (m, 1H), 4.04 (s, 3H), 7.17 (d, *J* = 8.5 Hz, 2H), 7.23 (d, *J* = 7.9 Hz, 1H), 7.30 (d, *J* = 8.4 Hz, 2H), 7.43 (t, *J* = 7.9 Hz, 2H), 9.61 (br s, 1H); ESIMS *m/e* 354 (M^++1, ^{35}Cl), 356 (M^++1, ^{37}Cl);

Elemental Analyses for $C_{20}H_{16}ClNO_3$:

Calculated: C, 67.90; H, 4.56; N, 3.96.

Found: C, 68.14; H, 4.51; N, 3.90.

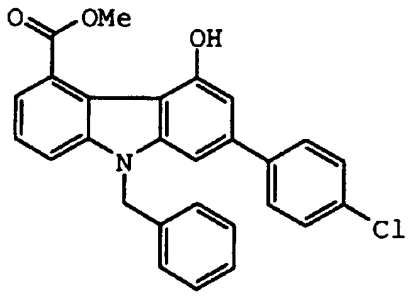
C. Preparation of 5-carbomethoxy-1,2-dihydro-2-(4-chlorophenyl)- 9-(phenylmethyl)carbazol-4(3H)-one



Prepared by the procedure of Example 17E in 90% yield. ^{1}H NMR ($CDCl_3$) δ 2.79 (d, J = 3.7 Hz, 1H), 2.82 (s, 1H), 2.97 (dd, J = 16.7, 11.5 Hz, 1H), 3.19 (dd, J = 16.7, 4.7 Hz, 1H), 3.59 (m, 1H), 4.06 (s, 3H), 5.35 (s, 2H), 6.96 (t, J = 3.6 Hz, 2H), 7.21 (m, 2H), 7.30 (m, 6H), 7.36 (t, J = 7.5 Hz, 2H); ESIMS m/e 444 (M^++1, ^{35}Cl), 446 (M^++1, ^{37}Cl); Elemental Analyses for $C_{27}H_{22}ClNO_3$:

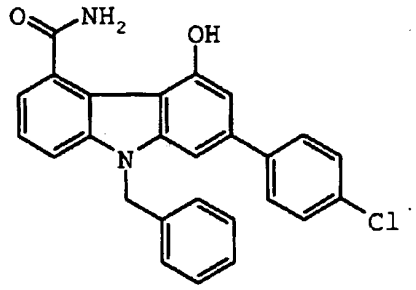
Calculated:	C, 73.05; H, 5.00; N, 3.16.
Found:	C, 73.23; H, 5.15; N, 3.36.

D. Preparation of 5-carbomethoxy-2-(4-chlorophenyl)-4-hydroxy-9-(phenylmethyl)carbazole



Prepared by method of example 17(b) in 66% yield. ^{1}H NMR ($CDCl_3$) δ 4.12 (s, 3H), 5.60 (s, 2H), 7.10 (t, J = 4.5 Hz, 4H), 7.32 (m, 3H), 7.41 (m, 3H), 7.60 (d, J = 8.5 Hz, 3H), 8.04 (d, J = 7.2 Hz, 1H).

E. Preparation of 5-carbamoyl-2-(4-chlorophenyl)-4-hydroxy-9-(phenylmethyl)carbazole



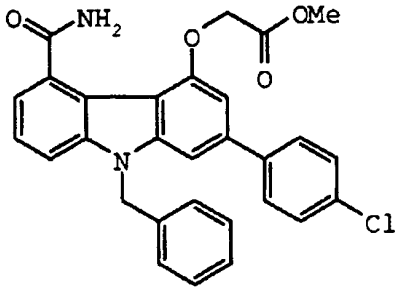
Prepared by the procedure of example Example 17G in 43% yield. ^{1}H NMR ($CDCl_3$) δ 5.77 (s, 2H), 6.89 (s, 1H), 7.07 (d, J = 7.0 Hz, 2H), 7.23 (m, 3H), 7.45 (m, 5H), 7.76 (d, J = 8.4 Hz, 3H), 8.40 (s, 1H), 8.85 (s, 1H); ESIMS *m/e* 427 (M^++1, ^{35}Cl), 429 (M^++1, ^{37}Cl);

Elemental Analyses for $C_{26}H_{19}ClN_2O_2$:

calculated: C, 73.15; H, 4.49; N, 6.56.

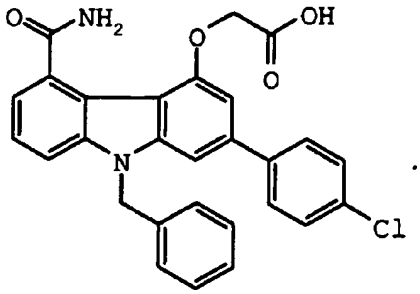
Found: C, 72.92; H, 4.57; N, 6.46.

F. Preparation of [5-carbamoyl-2-(4-chlorophenyl)-9-(phenylmethyl)carbazol-4-yl]oxyacetic acid, methyl ester



Prepared by the procedure of example Example 17H in 79% yield. ^{1}H NMR ($CDCl_3$) δ 3.84 (s, 3H), 4.97 (s, 2H), 5.57 (s, 2H), 6.08 (br s, 1H), 6.14 (br s, 1H), 6.74 (s, 1H), 7.12 (m, 2H), 7.18 (s, 1H), 7.22 (m, 2H), 7.41 (m, 6H), 7.51 (d, J = 8.5 Hz, 2H); ESIMS *m/e* 499 (M^++1, ^{35}Cl), 501 (M^++1, ^{37}Cl).

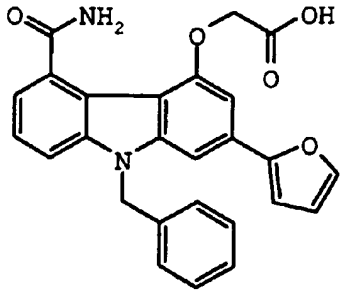
G. Preparation of [5-carbamoyl-2-(4-chlorophenyl)-9-(phenylmethyl)carbazol-4-yl]oxyacetic acid



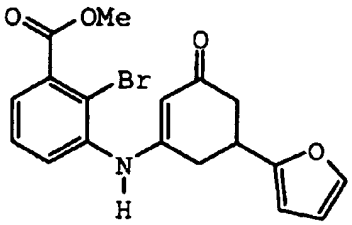
Prepared by the procedure of example Example 17I in 100% yield. ^{1}H NMR ($CDCl_3$) δ 4.95 (s, 2H), 5.75 (s, 2H), 6.88 (s, 1H), 7.20 (m, 4H), 7.52 (m, 6H), 7.76 (m, 3H), 12.92 (s, 1H); ESIMS *m/e* 485 (M^++1, ^{35}Cl), 487 (M^++1, ^{37}Cl).

Example 22

[5-carbamoyl-2-(2-furyl)-9-(phenylmethyl)carbazol-4-yl]oxyacetic acid



A. Preparation of 3-(2-bromo-3-carbomethoxyanilino)-5-(2-furyl)cyclohex-2-en-1-one



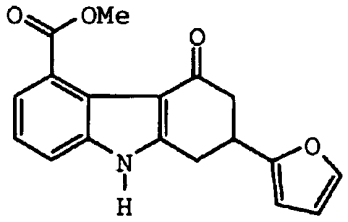
Prepared in 55% yield by the method of Example 17, part C. IR (KBr) 3201, 1735, 1593, 1575 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.56-2.94 (m, 4H), 3.53-3.60 (m, 1H), 3.94 (s, 1H), 5.60 (s, 1H), 6.11 (d, *J* = 2.8Hz, 1H), 6.22 (br s, 1H), 6.32-6.34 (m, 1H), 7.34-7.39 (m, 1H), 7.37 (br s, 1H), 7.55 (d, *J* = 7.9 Hz, 2H); *m/e* 390 (M^++1, ^{79}Br), 392 (M^++1, ^{81}Br);

Elemental Analyses for $C_{18}H_{16}BrNO_4$:

Calculated: C, 55.40; H, 4.13; N, 3.59.

Found: C, 55.62; H, 4.27; N, 3.71.

B. Preparation of 5-carbomethoxy-1,2-dihydro-2-(2-furyl)-9H-carbazol-4(3H)-one



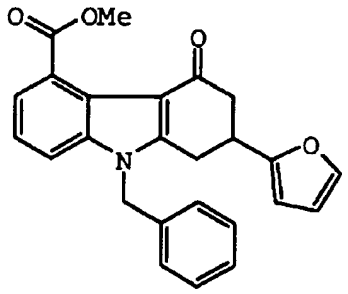
Prepared by the method of Example 17D in 47% yield. IR (KBr) 1736, 1633 cm^{-1}; ^1H NMR (THF-d_8): δ 2.59-2.77 (m, 2H), 3.14 (dd, *J* = 16.5, 10.5 Hz, 1H), 3.30 (dd, *J* = 16.5, 10.3 Hz, 1H), 3.56-3.69 (m, 1H), 3.81 (s, 3H), 6.13-6.14 (m, 1H), 6.27-6.29 (d, *J* = 2.5 Hz, 1H), 7.11-7.21 (m, 2H), 7.37-7.39 (m, 1H), 7.39 (s, 1H), 11.03 (br s, 1H); ESIMS *m/e* 310 (M^++1);

Elemental Analyses for $C_{18}H_{15}NO_4 \bullet 0.1C_7H_8$:

Calculated: C, 70.51; H, 4.50; N, 4.40.

Found: C, 70.75; H, 4.85; N, 4.61.

C. Preparation of 5-carbomethoxy-1,2-dihydro-2-(2-furyl)-9-(phenylmethyl)carbazol-4(3H)-one

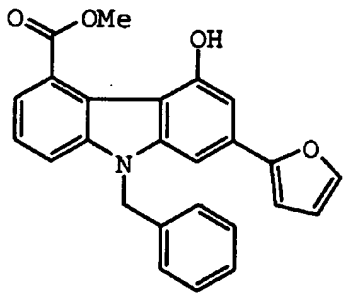


Prepared in 91% yield by the method of Example 17E. IR (KBr) 3500 (br), 1722, 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.79 (dd, J = 16.6, 10.8 Hz, 1H), 2.94 (dd, J = 16.6, 4.2 Hz, 1H), 3.06 (dd, J = 16.8, 9.8 Hz, 1H), 3.31 (dd, J = 18.8, 4.7 Hz, 1H), 3.68-3.74 (m, 1H), 4.06 (s, 3H), 5.37 (s, 2H), 6.08 (d, J = 2.7 Hz, 1H), 6.28 (m, 1H), 6.96 (m, 2H), 7.22-7.40 (m, 7H); ESIMS m/e 400 (M^++1);

Elemental Analysis for $C_{25}H_{21}NO_4$:

Calculated:	C, 75.17; H, 5.30; N, 3.51.
Found:	C, 75.46; H, 5.32; N, 3.67.

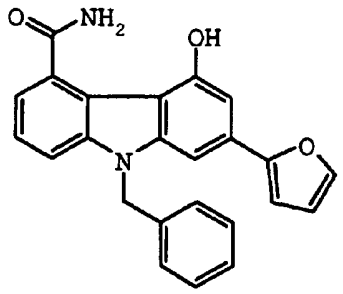
D. Preparation of 5-carbomethoxy-2-(2-furyl)-4-hydroxy-9-(phenylmethyl)carbazole



Prepared in 72% yield by the method (b) of Example 17F. IR (KBr) 3500 (br), 1674 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.11 (s, 3H), 5.58 (s, 2H), 6.48-6.50 (m, 1H), 6.75 (d, J = 3.2 Hz, 1H), 7.09-7.12 (m, 2H), 7.16 (s, 1H), 7.26-7.30 (m, 4H), 7.36-

7.44 (t, J = 8.0 Hz, 1H), 7.48 (s, 1H), 7.56 (d, J = 8.1 Hz, 1H), 8.01 (d, J = 7.5 Hz, 1H), 10.50 (br s, 1H); ESIMS m/e 398 (M^++1).

E. Preparation of 5-carbamoyl-2-(2-furyl)-4-hydroxy-9-(phenylmethyl)carbazole



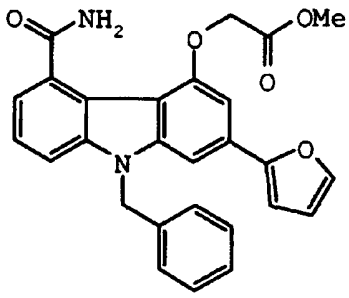
Prepared in 60% yield by the method of Example 17G. IR (KBr) 3425 (br), 3325 (br), 1642, 1628 cm^{-1}; ^1H NMR (DMSO-d_6) δ 5.72 (s, 2H), 6.56-6.57 (m, 1H), 6.95 (s, 1H), 6.98 (d, J = 3.0 Hz, 1H), 7.07 (d, J = 7.2 Hz, 2H), 7.17-7.26 (m, 3H), 7.42-7.43 (m, 3H), 7.71-7.76 (m, 2H), 8.38 (s, 1H), 8.83 (s, 1H), 10.70 (s, 1H); ESIMS m/e 381 (M^--1);

Elemental Analyses for $C_{24}H_{18}N_2O_3$:

Calculated: C, 75.38; H, 4.74; N, 7.33.

Found: C, 75.35; H, 4.95; N, 7.29.

F. Preparation of [5-carbamoyl-2-(2-furyl)-9-(phenylmethyl)carbazol-4-yl]oxyacetic acid, methyl ester



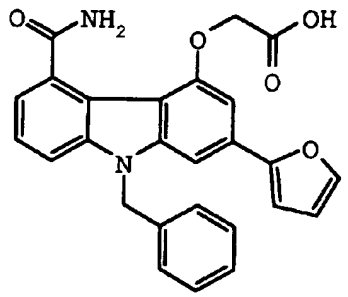
Prepared in 80% yield by the method of Example 17H. IR (KBr) 3358, 1756, 1643 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.70 (s, 3H), 4.98 (s, 2H), 5.70 (s, 2H), 6.58 (d, *J* = 1.5 Hz, 1H), 6.93 (s, 1H), 7.01-7.30 (m, 8H), 7.35 (t, *J* = 7.7 Hz, 1H), 7.51-7.57 (m, 3H), 7.72 (s, 1H); ESIMS *m/e* 455 (M^++1);

Elemental Analyses for $C_{27}H_{22}N_2O_5$:

Calculated: C, 71.36; H, 4.88; N, 6.16.

Found: C, 71.46; H, 4.91; N, 6.24.

G. Preparation of [5-carbamoyl-2-(2-furyl)-9-(phenylmethyl)carbazol-4-yl]oxyacetic acid



Prepared in 88% yield by the method of Example 17I. ^1H NMR (DMSO-d_6) δ 4.89 (s, 2H) 5.71 (s, 2H), 6.58 (s, 1H), 6.94 (s, 1H), 7.00-7.38 (m, 9H), 7.59 (d, *J* = 9.2 Hz, 1H), 7.58 (s, 1H), 7.72 (br s, 2H), 12.98 (br s, 1H); ESIMS *m/e* 441 (M^++1);

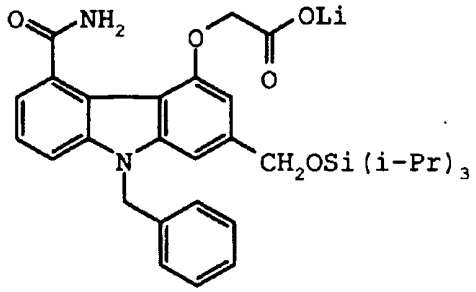
Elemental Analyses for $C_{26}H_{20}N_2O_5$:

Calculated: C, 70.90; H, 4.58; N, 6.36.

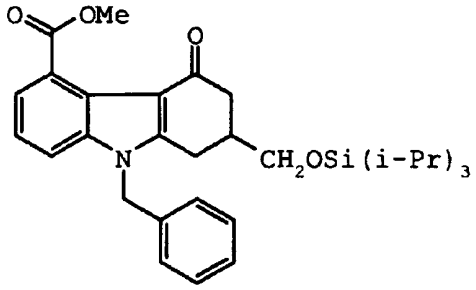
Found: C, 71.20; H, 4.67; N, 6.28.

Example 23

[5-carbamoyl-9-(phenylmethyl)-2-[(tri(-1-methylethyl)silyl)oxymethyl]carbazol-4-yl]oxyacetic acid, lithium salt



A. Preparation of 5-carbomethoxy-1,2-dihydro-9-(phenylmethyl)-2-[(tri(-1-methylethyl)silyl)oxymethyl]carbazol-4(3H)-one



Triisopropylsilyl trifluoromethanesulfonate (2.46 mL, 9.15 mmol) was added to a stirred suspension of the compound of Example 19C (2.89 g, 7.95 mmol) and anhydrous pyridine (0.964 mL, 11.9 mmol) in anhydrous methylene chloride (29 mL) at 0 °C under a nitrogen atmosphere. The mixture was stirred at 0 °C for 1 hour. Methanol (0.5 mL) was added to the mixture and stirring was continued for 1 minute. After dilution with toluene (10 mL), the mixture was concentrated and the residue was subject to chromatographic purification on silica (gradient 10-50% ethyl acetate in hexane) to give subtitled compound (4.06 g, 98%) as a white solid. IR (KBr) 1725, 1645 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90-1.15 (m, 21H, -$CH(CH_3)_2$), 2.50-2.63 (m, 3H), 2.74-2.86 (m, 1H), 3.02 (br d,

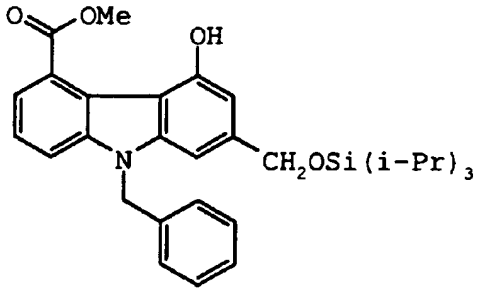
J = 7.7 Hz, 1H), 3.67-3.81 (m, 2H, $-CH_2O-$), 4.05 (s, 3H, $-OCH_3$), 5.37 (s, 2H, $-NCH_2-$), 7.00-7.04 (m, 2H), 7.22-7.44 (m, 6H); ESIMS *m/e* 520 (M^++1);

Elemental Analyses for $C_{31}H_{41}NO_4Si$:

Calculated: C, 71.64; H, 7.95; N, 2.69.

Found: C, 71.75; H, 7.91; N, 2.82.

B. Preparation of 5-carbomethoxy-4-hydroxy-9-(phenylmethyl)-2-[(tri(-1-methylethyl)silyl)oxymethyl]carbazole



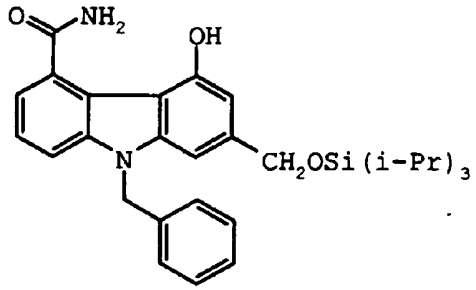
Following the experimental procedure (b) as described in the synthesis of Example 17F, subtitled compound was obtained as a yellowish solid in a 93% yield. IR (KBr) 3165 (br), 1671, 1629 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.00-1.22 (m, 21H, $-CH(CH_3)_2$), 4.10 (s, 3H, $-OCH_3$), 4.97 (s, 2H, $-OCH_2-$), 5.51 (s, 2H, $-NCH_2-$), 6.79 (s, 1H), 7.05-7.14 (m, 3H), 7.20-7.30 (m, 3H), 7.39 (t, J = 8.0 Hz, 1H), 7.59 (d, J = 8.0 Hz, 1H), 7.98 (d, J = 8.0 Hz, 1H), 10.50 (s, 1H, -OH); ESIMS *m/e* 518 (M^++1);

Elemental Analyses for $C_{31}H_{39}NO_4Si$:

Calculated: C, 71.92; H, 7.59; N, 2.71.

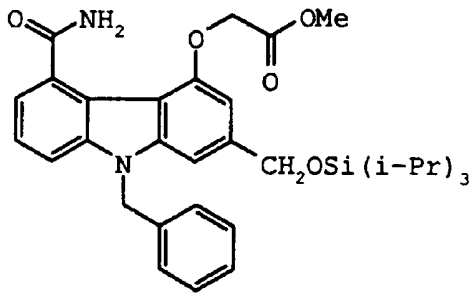
Found: C, 72.19; H, 7.21; N, 2.76.

C. Preparation of 5-carbamoyl-4-hydroxy-9-(phenylmethyl)-2-[(tri(-1-methylethyl)silyl)oxymethyl]carbazole



Following the experimental procedure as described in the synthesis of Example 17F(b), subtitled compound was obtained as a yellowish solid in a 80% yield. IR (KBr) 3348 (br), 3200, 1660, 1628 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.00-1.20 (m, 21H, $-CH(CH_3)_2$), 4.94 (s, 2H, $-OCH_2-$), 5.52 (s, 2H, $-NCH_2-$), 6.22 (s, 1H, -NH), 6.56 (s, 1H, -NH), 6.75 (s, 1H), 7.05-7.10 (m, 3H), 7.20-7.28 (m, 3H), 7.36 (t, J = 7.6 Hz, 1H), 7.43 (d, J = 7.6 Hz, 1H), 7.53 (d, J = 7.6 Hz, 1H), 9.75 (br s, 1H, -OH); ESIMS m/e 503 (M^++1).

D. Preparation of [5-carbamoyl-9-(phenylmethyl)-2-[(tri(-1-methylethyl)silyl)oxymethyl]carbazol-4-yl]oxyacetic acid, methyl ester



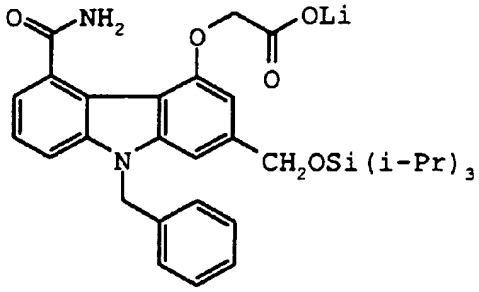
Following the experimental procedure as described in the synthesis of Example 17H, subtitled produce was obtained as a white solid in a 94% yield. IR (KBr) 3484, 3180 (br), 1764, 1675 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.00-1.20 (m, 21H, $-CH(CH_3)_2$), 3.82 (s, 3H, $-OCH_3$), 4.89 (s, 2H, $-OCH_2-$), 4.93

(s, 2H, $-OCH_2-$), 5.50 (s, 2H, $-NCH_2-$), 6.00 (br s, 2H, $-NH_2$), 6.60 (s, 1H), 7.05-7.12 (m, 3H), 7.22-7.28 (m, 3H), 7.32-7.38 (m, 1H), 7.39-7.41 (m, 2H); ESIMS *m/e* 575 (M^++1); Elemental Analyses for $C_{33}H_{42}N_2O_5Si$:

Calculated: C, 68.96; H, 7.37; N, 4.87.

Found: C, 69.14; H, 7.20; N, 4.95.

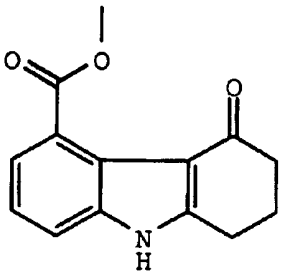
E. Preparation of [5-carbamoyl-9-(phenylmethyl)-2-[(tri(-1-methylethyl)silyl)oxymethyl]carbazol-4-yl]oxyacetic acid, lithium salt



Lithium hydroxide (4.17 N, 42.5 *m*L, 0.177 mmol) was added to a stirred suspension of part D above (50.9 mg, 0.0886 mmol) in THF (1 mL)/CH_3OH (0.3 mL)/H_2O (0.3 mL). The resultant mixture was stirred in an oil bath at 55 °C for 1 hour to form a white suspension. At ambient temperature, the white suspension was diluted with water (5 mL) and THF was evaporated *in vacuo*. After filtration and washing with water, the white solid was dried under vacuum to give 11 (40.0 mg, 80%) of the title product. IR (KBr) 3470, 3315, 1652, 1621 cm^{-1}; ^1H NMR (DMSO-d_6) δ 0.90-1.15 (m, 21H, $-CH(CH_3)_2$), 4.29 (s, 2H, $-OCH_2-$), 4.84 (s, 2H, $-OCH_2-$), 5.57 (s, 2H, $-NCH_2-$), 6.49 (s, 1H), 7.00-7.25 (m, 7H), 7.31 (br t, *J* = 7.9 Hz, 1H), 7.43 (br s, 1H, -NH), 7.59 (br d, *J* = 7.9 Hz, 1H), 7.72 (br s, 1H, -NH); ESIMS *m/e* 567 (M^++1).

Preparation 3

Preparation of 5-Carbomethoxy-1,2-dihydro-9H-carbazol-4(3H)-one from 2-chloro-3-nitrobenzoic acid



a) Methyl 2-chloro-3-nitrobenzoate

A solution of 2-chloro-3-nitrobenzoic acid (20.16 g, 100.0 mM), iodomethane (15.6 g, 110 mM), and potassium carbonate (15.0 g, 108.5 mM) in 100 mL DMF was stirred at room temperature for 48 hours. The mixture was poured into 1.5 liters of H_2O. The resultant precipitate was collected by 20.0 g (93%) of methyl 2-chloro-3-nitrobenzoate as a white solid. ^1H NMR ($CDCl_3$) δ 8.42 (dd, 1H, J=1 and 8 Hz), 8.18 (dd, 1H, J=1 and 8 Hz), 7.43 (t, 1H, J=8 Hz), and 3.9 (s, 3H). IR (KBr, cm^{-1}) 1743, 1719, 1595, 1540, 1532, 1433, 1357, 1300, and 730. MS (FD) m/e 215, 216.

Elemental Analyses for $C_8H_6NO_4Cl$:

Calculated: C, 44.57; H, 3.81; N, 6.50.

Found: C, 44.19; H, 3.45; N, 6.19.

b) Methyl 2-chloro-3-aminobenzoate

Hydrogen gas was passed through a solution of methyl 2-chloro-3-nitrobenzoate (10.0 g, 46.4 mM) and 1.0 g of 3% sulfided platinum on carbon in 150 mL ethyl acetate for 48 hours at room temperature. The catalyst was removed by filtration through celite. Concentration of the filtrate afforded 8.6 g (100%) of methyl 2-chloro-3-aminobenzoate as a yellow oil. ^1H NMR ($CDCl_3$) δ 7.25 (dd, 1H, J=1 and 8 Hz), 7.2 (t, 1H, J=8 Hz), 6.95 (dd, 1H, J=1 and 8 Hz), and 3.9

(s, 3H). IR ($CHCl_3$, cm^{-1}) 3450, 3380, 2980, 2900, 1729, 1615, 1456, 1434, 1322, 1290, and 1268. MS (ES) m/e 186,188. Elemental Analyses for $C_8H_8NO_2Cl$:

Calculated: C, 51.77; H, 4.34; N, 7.55.

Found: C, 51.52; H, 4.17; N, 7.54.

b) Methyl 2-chloro-3-aminobenzoate

A solution of stannous chloride (27.0 g, 137.0 mM) in 55 mL of concentrated hydrochloric acid was slowly added to a solution of methyl 2-chloro-3-nitrobenzoate (6.0 g, 27.9 mM) in 75 mL ethanol at 15-20 °C over 1 hour. The mixture was then heated at 50-60 °C for 15 minutes. The mixture was cooled to room temperature and made alkaline by slow addition of solid sodium hydroxide maintaining a temperature of 30-35 °C. The resultant mixture was extracted three times with chloroform. The extracts were washed with brine, dried over sodium sulfate, filtered and concentrated to afford 2.6 g (50%) of methyl 2-chloro-3-aminobenzoate as a yellow oil, identical in all respects to the material derived via catalytic hydrogenation described above.

b) Methyl 2-chloro-3-aminobenzoate

A solution of sodium dithionite (14.0 g, 20.0 mM) and sodium carbonate (6.7 g) in 200 mL of water was slowly added to a solution of methyl 2-chloro-3-nitrobenzoate (6.0 g, 27.9 mM) in 40 mL methanol and 40 mL of tetrahydrofuran at 25 °C over 30 minutes. The mixture was stirred at room temperature for an additional 30 minutes, then extracted with ethyl acetate. The extracts were washed with brine, dried over sodium sulfate, filtered and concentrated to afford 1.2 g (33%) of methyl 2-chloro-3-aminobenzoate as a yellow oil, identical in all respects to the material derived via catalytic hydrogenation described above.

c) 3-(3-Carbomethoxy-2-chloroanilino)cyclohex-2-en-1-one

A mixture of methyl 2-chloro-3-aminobenzoate (11.11 g, 59.86 mM) and 1,3-cyclohexanedione (9.05 g, 80.8 mM) was heated at 120 °C under a stream of nitrogen for 4 hours. The resultant solid was triturated with hot ethyl acetate, then dried *in vacuo* to afford 14.05 g (84%) of 3-(3-carbomethoxy-2-chloroanilino)cyclohex-2-en-1-one as a yellow orange solid. ^{1}H NMR ($CDCl_3$) δ 7.6 (dt, 1H, J=1 and 8 Hz), 7.3 (t, 1H, J=8 Hz), 6.6 (br s, 1H), 5.62 (s, 1H), 3.95 (s, 3H), 2.6 (t, 2H, J=6 Hz), 2.4 (t, 2H, J=6 Hz), and 2.1 (m, 2H). IR ($CHCl_3$, cm^{-1}) 3050, 2950, 1729, 1536, 1351, 1299, 1290, 1267, and 1135. MS (ES) m/e 278, 280, 282.

Elemental Analyses for $C_{14}H_{14}NO_3Cl$:

Calculated: C, 60.11; H, 5.04; N, 5.01.

Found: C, 57.51; H, 4.99; N, 4.68.

d) 5-Carbomethoxy-1,2-dihydro-9H-carbazol-4(3H)-one

A suspension of 3-(3-carbomethoxy-2-chloroanilino)cyclohex-2-en-1-one (10.22 g, 36.67 mM), palladium acetate (0.82 g, 3.66 mM), tricyclohexylphosphine (4.10 g, 14.62 mM), and triethylamine (30.0 mL, 21.78 g, 215.2 mM) in 100 mL acetonitrile was heated at 130 °C in a sealed vessel for 14 days. The mixture was diluted with ethyl acetate, washed twice with 1 N HCl, twice with H_2O, once with saturated brine, dried over anhydrous magnesium sulfate, filtered, and concentrated to afford 9.9 g of a light brown gum. Purification by HPLC on silica gel (elution with gradient methylene chloride/ethyl acetate) afforded 4.68 g (52%) of the 5-carbomethoxy-1,2-dihydro-9H-carbazol-4(3H)-one as a yellow solid. ^{1}H NMR ($CDCl_3$) δ 9.15 (br s, 1H), 7.4 (dd, 1H, J=1 and 8 Hz), 7.35 (dd, 1H, J=1 and 8 Hz), 7.25 (t, 1H, J=8 Hz), 4.05 (s, 3H), 2.95 (t, 2H, J=6 Hz), 2.55 (t, 2H, J=6 Hz), and 2.2 (m , 2H). IR ($CHCl_3$, cm^{-1})

3400, 3200 (br), 3000, 2950, 1721, 1646, 1466, 1439, 1427, 1299, 1284, 1165, and 1135. MS (ES) m/e 242, 244.

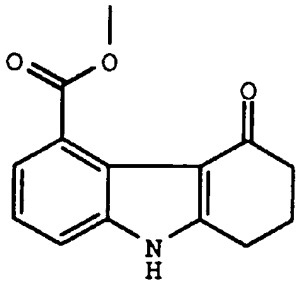
Elemental Analyses for $C_{14}H_{13}NO_3$:

Calculated: C, 69.12; H, 5.39; N, 5.76.

Found: C, 68.82; H, 5.67; N, 5.60.

Preparation 4

Preparation of 5-Carbomethoxy-1,2-dihydro-9H-carbazol-4(3H)-one from 2-bromo-3-nitrobenzoic acid



a) Methyl 2-bromo-3-nitrobenzoate

A solution of 2-bromo-3-nitrobenzoic acid (28.4 g, 115.0 mM), iodomethane (18.0 g, 127 mM), and potassium carbonate (19.0 g, 137.4 mM) in 100 mL DMF was stirred at room temperature for 72 hours. The mixture was poured into 1.5 liters of H_2O. The resultant precipitate was collected by filtration and dried *in vacuo* to afford 28.79 g (96%) of methyl 2-bromo-3-nitrobenzoate as a white solid. ^1H NMR (DMSO-d6) δ 8.3 (dd, 1H, J=1 and 8 Hz), 7.9 (dd, 1H, J=1 and 8 Hz), 7.7 (t, 1H, J=8 Hz), and 3.9 (s, 3H). IR (KBr, cm^{-1}) 2950, 1738, 1541, 1435, 1364, 1298, and 1142. MS (FD) m/e 259, 261.

Elemental Analyses for $C_8H_6NO_4Br$:

Calculated: C, 36.95; H, 2.33; N, 5.39.

Found: C, 37.14; H, 2.37; N, 5.45.

b) Methyl 2-bromo-3-aminobenzoate

Hydrogen gas was passed through a solution of methyl 2-bromo-3-nitrobenzoate (0.20 g, 0.77 mM) and 0.1 g of 3% sulfided platinum on carbon in 25 mL ethyl acetate for 24 hours at room temperature. The catalyst was removed by filtration through celite. Concentration of the filtrate afforded 0.175 g (99%) of methyl 2-bromo-3-aminobenzoate as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 7.15 (t, 1H, J=8 Hz), 7.1 (dd, 1H, J=1 and 8 Hz), 6.8 (dd, 1H, J=1 and 8 Hz), and 3.95 (s, 3H). IR ($CHCl_3$, cm^{-1}) 3550, 3380, 2980, 2900, 1729, 1613, 1465, 1451, 1434, 1324, 1266, and 1025. MS (FD) m/e 230, 232.

Elemental Analyses for $C_8H_8NO_2Br$:

Calculated: C, 41.77; H, 3.51; N, 6.09.

Found: C, 42.01; H, 3.29; N, 6.00.

b) Methyl 2-bromo-3-aminobenzoate

A solution of stannous chloride (15.0 g, 76.1 mM) in 30 mL of concentrated hydrochloric acid was slowly added to a solution of methyl 2-bromo-3-nitrobenzoate (4.0 g, 15.4 mM) in 90 mL ethanol at 15-30 °C over 1 hour. The mixture was then heated at 50-60 °C for 15 minutes. The mixture was cooled to room temperature and made alkaline by slow addition of solid sodium hydroxide maintaining a temperature of 30-35 °C. The resultant mixture was extracted three times with chloroform. The extracts were washed with brine, dried over sodium sulfate, filtered and concentrated to afford 3.51 g (99%) of methyl 2-bromo-3-aminobenzoate as a yellow oil, identical in all respects to the material derived via catalytic hydrogenation described above.

c) 3-(3-Carbomethoxy-2-bromoanilino)cyclohex-2-en-1-one

A mixture of methyl 2-bromo-3-aminobenzoate (13.2 g, 60.0 mM) and 1,3-cyclohexanedione (8.4 g, 75 mM) was heated

at 125 °C under a stream of nitrogen for 4 h. The resultant solid was purified by HPLC on silica gel (elution with methylene chloride/ethyl acetate) to afford 17.2 g (88%) of 3-(3-carbomethoxy-2-bromoanilino)cyclohex-2-en-1-one as a tan foam. ^{1}H NMR (DMSO-d6) δ 8.75 (s, 1H), 7.6-7.4 (m, 3H), 4.65 (s, 1H), 3.85 (s, 3H), 2.6 (t, 2H, J=6 Hz), 2.15 (t, 2H, J=6 Hz), and 1.9 (m, 2H). IR ($CHCl_3$, cm^{-1}) 3400, 3004, 2954, 1732, 1607, 1588, 1573, 1513, 1464, 1436, 1412, 1308, 1249, 1177, and 1144. MS (ES) m/e 322, 324, 326.

Elemental Analyses for $C_{14}H_{14}NO_3Br$:

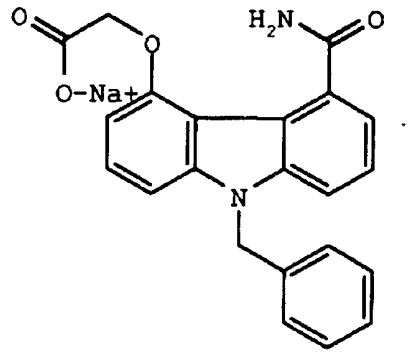
Calculated:	C, 51.85;	H, 4.32; N, 4.32.
Found:	C, 53.60;	H, 4.73; N, 4.09.

d) 5-Carbomethoxy-1,2-dihydro-9H-carbazol-4(3H)-one

A suspension of 3-(3-carbomethoxy-2-bromoanilino)cyclohex-2-en-1-one (15.8 g, 48.8 mM), palladium acetate (1.12 g, 5.0 mM), tri-*o*-tolylphosphine (3.1 g, 10.0 mM), and triethylamine (6.3 g, 62.0 mM) in 120 mL acetonitrile was heated at reflux for 8 hours. The solvent was removed *in vacuo*. The residue was dissolved in methylene chloride, washed twice with 1 N HCl, twice with H_2O, once with saturated brine, dried over anhydrous magnesium sulfate, filtered, and concentrated to afford 17 g of a light brown foam. Purification by HPLC on silica gel (elution with gradient methylene chloride/ethyl acetate) afforded 9.2 g (78%) of the 5-carbomethoxy-1,2-dihydro-9H-carbazol-4(3H)-one as a yellow solid, identical with the material derived from 3-(3-carbomethoxy-2-chloroanilino)cyclohex-2-en-1-one, described above. ^{1}H NMR (DMSO-d6) δ 7.5 (d, 1H, J=8 Hz), 7.25-7.1 (m, 2H), 5.7 (s, 1H), 3.8 (s, 3H), 2.95 (t, 2H, J=6 Hz), 2.4 (t, 2H, J=6 Hz), and 2.1 (m , 2H). MS (ES) m/e 242, 244.

EXAMPLE 24

Preparation of {9-[(phenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, sodium salt



A. 9-[(Phenyl)methyl]-5-carbomethoxy-1,2-dihydrocarbazol-4(3H)-one

A suspension of 5-carbomethoxy-1,2-dihydro-9H-carbazol-4(3H)-one (300 mg, 1.23 mM), benzyl bromide (210 mg, 1.23 mM), and potassium carbonate (170 mg, 1.23 mM) in 15 mL DMF was stirred at room temperature for 6 hours. The mixture was diluted with 80 mL H_2O and chilled in the refrigerator. The resultant white precipitate was collected by filtration, washed with H_2O, and dried *in vacuo* to afford 325 mg (79%) of the 9-[(phenyl)methyl]-5-carbomethoxy-1,2-dihydrocarbazol-4(3H)-one as a white solid. ^{1}H NMR (DMSO-d6) δ 7.7 (dd, 1H, J=1 and 8 Hz), 7.45-7.0 (m, 7H), 5.6 (s, 2H), 3.8 (s, 3H), 3.05 (t, 2H, J=6 Hz), 2.5 (t, 2H, J=6 Hz), and 2.2 (m , 2H). IR (KBr, cm^{-1}) 3421, 1726, 1676, 1636, 1473, 1450, 1435, 1288, 1122, 764, 745, and 706. MS (ES) m/e 334.

Elemental Analyses for $C_{21}H_{19}NO_3$:

Calculated: C, 75.68; H, 5.71; N, 4.20.

Found: C, 70.85; H, 5.53; N, 4.49.

B. 9-[(Phenyl)methyl]-4-hydroxy-5-carbomethoxy carbazole

(a) A solution of the 9-[(phenyl)methyl]-5-carbomethoxy-1,2-dihydrocarbazol-4(3H)-one (1.5 g, 4.5 mM) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (1.12 g, 5.0 mM) in 25 mL of toluene was stirred between 80-90 °C for 6 h. The mixture was purified directly by column chromatography on silica gel (elution with methylene chloride/ethyl acetate) to afford 420 mg (28%) of the 9-[(phenyl)methyl]-4-hydroxy-5-carbomethoxy carbazole as a yellow solid. ^{1}H NMR (DMSO-d6) δ 10.25 (s, 1H), 7.7 (d, 1H, J=8 Hz), 7.4 (t, 1H, J=8 Hz), 7.4-7.0 (m, 8H), 6.6 (d, 1H, J=8 Hz), 5.6 (s, 2H), and 3.8 (s, 3H). IR ($CHCl_3$, cm^{-1}) 1723, 1685, 1621, 1597, 1568, 1496, 1453, 1442, 1392, 1286, 1267, 1156, and 1138. MS (ES) m/e 330, 332.

Elemental Analyses for $C_{21}H_{17}NO_3$:

Calculated:	C, 76.13; H, 5.14; N, 4.23.
Found:	C, 75.90; H, 5.20; N, 4.46.

(b) To a solution of the 9-[(phenyl)methyl]-5-carbomethoxy-1,2-dihydrocarbazol-4(3H)-one (2.87 g, 8.61 mM) in 29 ml dioxane was added 60% sodium hydride in mineral oil (0.79 g, 19.8 mM). The reaction was stirred 8 minutes, then methyl benzenesulfinate (1.80 ml, 13.8 mM) was added. The reaction was stirred an additional 1.5 h, then diluted with 43 ml dioxane and 1.13 ml acetic acid. The mixture was refluxed 1 h, diluted with ethyl acetate, and extracted with sat'd $NaHCO_3$ two times, then with brine. After drying ($NaSO_4$), evaporation in vacuo afforded 4.90 g. The mixture was purified by column chromatography on silica gel (elution with toluene/methylene chloride) to afford 2.31 g (81%) of the 9-[(phenyl)methyl]-4-hydroxy-5-carbomethoxy carbazole. ^{1}H NMR (DMSO-d6) δ 10.25 (s, 1H), 7.7 (d, 1H, J=8 Hz), 7.4 (t, 1H, J=8 Hz), 7.4-7.0 (m, 8H), 6.6 (d, 1H, J=8 Hz), 5.6

(s, 2H), and 3.8 (s, 3H). IR ($CHCl_3$, cm^{-1}) 1723, 1685, 1621, 1597, 1568, 1496, 1453, 1442, 1392, 1286, 1267, 1156, and 1138. MS (ES) m/e 330, 332.

Elemental Analyses for $C_{21}H_{17}NO_3$:

Calculated: C, 76.13; H, 5.14; N, 4.23.

Found: C, 75.90; H, 5.20; N, 4.46.

C. 9-[(Phenyl)methyl]-4-hydroxy-5-carbamoyl carbazole

A solution of the 9-[(phenyl)methyl]-4-hydroxy-5-carbomethoxy carbazole (200 mg, 0.6 mM) in 4 mL MeOH and 40 mL concentrated aqueous ammonium hydroxide was sonicated for 30 h at 40-50 °C. The mixture was diluted with ethyl acetate and acidified to pH 1 with 5 N HCl. The aqueous layer was extracted three times with ethyl acetate. The combined organic extracts were washed with saturated brine, dried over magnesium sulfate, filtered, and concentrated. The residue was purified by column chromatography on silica gel (elution with gradient methylene chloride/ethyl acetate) to afford 50 mg (26%) of the 9-[(phenyl)methyl]-4-hydroxy-5-carbamoyl carbazole as a white solid. ^1H NMR (DMSO-d6) δ 10.5 (s, 1H), 8.8 (br s, 1H), 8.4 (br s, 1H), 7.85 (dd, 1H, J=1 and 8 Hz), 7.5-7.1 (m, 9H), 6.6 (d, 1H, J=8 Hz), and 5.8 (s, 2H). IR (KBr, cm^{-1}) 3428, 3198, 3063, 1631, 1599, 1579, 1562, 1496, 1442, 1330, 1261, 1215, 775, and 697. MS (ES) m/e 315, 317.

Elemental Analyses for $C_{20}H_{16}N_2O_2$:

Calculated: C, 75.95; H, 5.06; N, 8.86.

Found: C, 74.88; H, 5.40; N, 7.78.

D. {9-[(Phenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, methyl ester

40% Methanolic Triton B (0.11 mL, 0.24 mM) was added to a solution of the 9-[(phenyl)methyl]-4-hydroxy-5-carbamoyl carbazole (70 mg, 0.22 mM) in 20 mL DMF at 0 °C. After 15

minutes, methyl bromoacetate (70 mg, 0.44 mM) was added and the resultant mixture stirred at room temperature for 5 h. The mixture was diluted with ethyl acetate, washed with 1 N HCl, H_2O, and saturated brine, dried over magnesium sulfate, filtered, and concentrated. The residue was combined with the crude material derived from a similar run utilizing 45 mg (0.14 mM [0.36 mM total]) of 9-[(phenyl)methyl]-4-hydroxy-5-carbamoyl carbazole. The combined residues were purified by column chromatography on silica gel (elution with ethyl acetate) to afford 76 mg (54%) of the {9-[(phenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, methyl ester as a white solid. ^{1}H NMR (DMSO-d6) δ 7.65 (d, 1H, J=8 Hz), 7.5 (br s, 1H), 7.4-7.15 (m, 9H), 7.1 (d, 1H, J=8 Hz), 6.6 (d, 1H, J=8 Hz), 5.7 (s, 2H), 4.9 (s, 2H), and 3.75 (s, 3H). IR (KBr, cm^{-1}) 3367, 3200, 1760, 1643, 1579, 1496, 1452, 1427, 1216, 1157, 772, and 716. MS (FD) m/e 388. Elemental Analyses for $C_{23}H_{20}N_2O_4$:

Calculated:	C, 71.13; H, 5.15; N, 7.22.
Found:	C, 70.77; H, 5.49; N, 6.79.

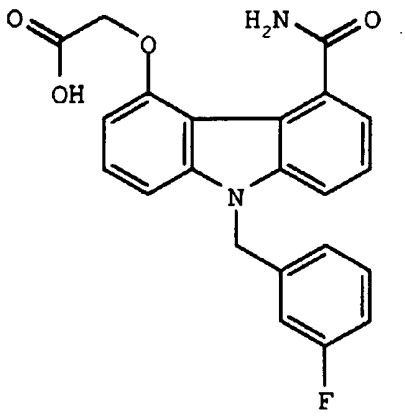
E. {9-[(Phenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, sodium salt.

A solution of the {9-[(phenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, methyl ester (10.1 mg, 0.025 mM) and 0.025 mL (0.025 mM) of 1 N NaOH in 3 mL of ethanol was stirred for 16 h at 25 °C. The resultant white precipitate was collected by filtration, washed with a small amount of EtOH, then dried *in vacuo* to afford 7.1 mg (70%) of the {9-[(phenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, sodium salt as a white powder. ^{1}H NMR (DMSO-d6) δ 7.6 (d, 1H, J=8 Hz), 7.5-7.05 (m, 11H), 6.55 (d, 1H, J=8 Hz), 5.75 (s, 2H), and 4.3 (s, 2H). IR (KBr, cm^{-1}) 3471, 1657, 1615, 1591, 1496, 1453, 1412, 1330, 1272, and 1151. MS (ES) m/e 373, 375, 397. Elemental Analyses for

$C_{22}H_{17}N_2O_4Na$: C, 66.67; H, 4.29; N, 7.07. Found C, 66.75; H, 4.55; N, 6.83.

EXAMPLE 25

Preparation of {9-[(3-fluorophenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid



A. 9-[(3-Fluorophenyl)methyl]-5-carbomethoxy-1,2-dihydrocarbazol-4(3H)-one

40% Methanolic Triton B (2.06 mL, 4.53 mM) was slowly added dropwise to a solution of 5-carbomethoxy-1,2-dihydro-9H-carbazol-4(3H)-one (930.0 mg, 3.82 mM) in 5 mL of DMF at 0 °C. After 5 minutes, 3-fluorobenzyl chloride (664.0 mg, 4.59 mM) was added and the resultant mixture stirred at 0 °C for 3 h, then at room temperature for 20 hours. The mixture was diluted with ethyl acetate, washed three times with 1 N HCl, three times with H_2O, once with saturated brine, dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue was purified by column chromatography on silica gel (elution with gradient methylene chloride/ethyl acetate) to afford 502.3 mg (37%) of the 9-[(3-fluorophenyl)methyl]-5-carbomethoxy-1,2-dihydrocarbazol-4(3H)-one as a yellow foam. ^1H NMR ($CDCl_3$) δ 7.4-7.2 (m, 4H), 6.9 (m, 1H), 6.7 (m, 2H), 5.35 (s, 2H), 4.05 (s, 3H), 2.9 (t, 2H, J=6 Hz), 2.65 (t, 2H, J=6 Hz), and

2.3 (m , 2H). IR ($CHCl_3$, cm^{-1}) 3050, 2950, 1725, 1654, 1464, 1451, 1440, 1288 and 1119. MS (ES) m/e 350, 352.

Elemental Analyses for $C_{21}H_{18}NO_3F$:

Calculated: C, 71.78; H, 5.16; N, 3.99.

Found: C, 72.00; H, 4.95; N, 4.11.

B. 9-[(3-Fluorophenyl)methyl]-4-hydroxy-5-carbomethoxy carbazole

A solution of the 9-[(3-fluorophenyl)methyl]-5-carbomethoxy-1,2-dihydrocarbazol-4(3H)-one (434.0 mg, 1.23 mM) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (324.0 mg, 1.42 mM) in 20 mL of toluene was stirred between 70-80 °C for 5 h. The mixture was purified directly by column chromatography on silica gel (elution with methylene chloride) to afford 137.0 mg (32%) of the 9-[(3-fluorophenyl)methyl]-4-hydroxy-5-carbomethoxy carbazole as a yellow foam. ^1H NMR (DMSO-d6) δ 10.2 (s, 1H), 7.7 (d, 1H, J=8 Hz), 7.4 (t, 1H, J=8 Hz), 7.3 (m, 2H), 7.2 (d, 1H, J=8 Hz), 7.1 (d, 1H, J=8 Hz), 7.05-6.85 (m, 3H), 6.6 (d, 1H, J=8 Hz), 5.65 (s, 2H), and 3.85 (s, 3H). IR ($CHCl_3$, cm^{-1}) 3200 (br), 1687, 1597, 1452, 1442, 1285, and 1267. MS (ES) m/e 348, 350.

Elemental Analyses for $C_{21}H_{16}NO_3F$:

Calculated: C, 72.20; H, 4.62; N, 4.01.

Found: C, 72.30; H, 4.66; N, 4.04.

C. 9-[(3-Fluorophenyl)methyl]-4-hydroxy-5-carbamoyl carbazole

A solution of the 9-[(3-fluorophenyl)methyl]-4-hydroxy-5-carbomethoxy carbazole (130.8 mg, 0.37 mM) in 5 mL THF and 20 mL concentrated aqueous ammonium hydroxide was sonicated for 5 h at 40-50 °C. The mixture was diluted with ethyl acetate and acidified to pH 1 with 5 N HCl. The aqueous layer was extracted twice with ethyl acetate. The combined

organic extracts were washed with saturated brine, dried over magnesium sulfate, filtered, and concentrated. The residue was purified by column chromatography on silica gel (elution with gradient methylene chloride/ethyl acetate) to afford 57.4 mg (45%) of the 9-[(3-fluorophenyl)methyl]-4-hydroxy-5-carbamoyl carbazole as a white solid. ^{1}H NMR (DMSO-d6) δ 10.5 (s, 1H), 8.8 (br s, 1H), 8.4 (br s, 1H), 7.8 (dd, 1H, J=1 and 8 Hz), 7.5 (m, 2H), 7.3 (m, 2H), 7.15-7.0 (m, 2H), 6.95 (d, 1H, J=8 Hz), 6.85 (d, 1H, J=8 Hz), 6.6 (d, 1H, J=8 Hz), and 5.7 (s, 2H). IR ($CHCl_3$, cm^{-1}) 3431, 3200 (br), 1628, 1614, 1600, 1580, 1546, 1488, 1448, 1329, 1261, and 776. MS (ES) m/e 333, 335.

Elemental Analyses for $C_{20}H_{15}N_2O_2F$:

Calculated: C, 71.85; H, 4.52; N, 8.38.

Found: C, 74.45; H, 6.01; N, 8.48.

D. {9-[(3-Fluorophenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, tert-butyl ester

40% Methanolic Triton B (0.086 mL, 0.19 mM) was added to a solution of the 9-[(3-fluorophenyl)methyl]-4-hydroxy-5-carbamoyl carbazole (51.9 mg, 0.155 mM) in 3 mL DMF at room temperature. After 3 minutes, t-butyl bromoacetate (87.8 mg, 0.44 mM) was added and the resultant mixture stirred at room temperature for 5 hours. The mixture was diluted with ethyl acetate, washed four times with H_2O, and saturated brine, dried over magnesium sulfate, filtered, and concentrated. The residue was purified by column chromatography on silica gel (elution with gradient methylene chloride/ethyl acetate) to afford 44.0 mg (63%) of the {9-[(3-fluorophenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, tert-butyl ester as a white solid. ^{1}H NMR (DMSO-d6) δ 7.6 (d, 1H, J=8 Hz), 7.5-6.8 (m, 10H), 6.55 (d, 1H, J=8 Hz), 5.7 (s, 2H), 4.8 (s, 2H), and 1.45 (s, 9H). IR ($CHCl_3$, cm^{-1}) 3450, 3400, 1746, 1674, 1592, 1457, 1369, and 1151. MS (FD) m/e 448.

Elemental Analyses for $C_{26}H_{25}N_2O_4F$:

Calculated: C, 69.63; H, 5.62; N, 6.25.

Found: C, 69.35; H, 5.44; N, 6.23.

E. {9-[(3-Fluorophenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid

A solution of the {9-[(3-fluorophenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, tert-butyl ester (40.0 mg, 0.089 mM) in 2 mL of trifluoroacetic acid was stirred at room temperature for 5 hours. The solvent was removed *in vacuo*. The residue was triturated with ethyl ether, then dried *in vacuo* to afford 35.0 mg (100%) of the {9-[(3-fluorophenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid as a white powder. ^{1}H NMR (DMSO-d6) δ 13.0 (br s, 1H), 7.75 (s, 1H), 7.6 (d, 1H, J=8 Hz), 7.5-7.25 (m, 5H), 7.2-6.8 (m, 4H), 6.6 (d, 1H, J=8 Hz), 5.7 (s, 2H), and 4.8 (s, 2H). IR (KBr, cm^{-1}) 3423, 3400, 1736, 1637, 1615, 1589, 1499, 1487, 1450, 1436, 1331, 1250, and 1156. MS (ES) m/e 391, 393.

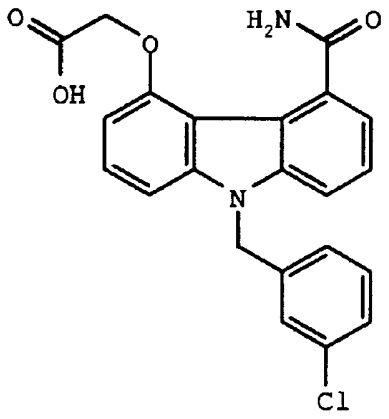
Elemental Analyses for $C_{22}H_{17}N_2O_4F$:

Calculated: C, 67.34; H, 4.37; N, 7.14.

Found: C, 67.63; H, 4.22; N, 7.35.

EXAMPLE 26

Preparation of {9-[(3-Chlorophenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid



A. 9-[(3-Chlorophenyl)methyl]-5-carbomethoxy-1,2-dihydrocarbazol-4(3H)-one

A suspension of 5-carbomethoxy-1,2-dihydro-9H-carbazol-4(3H)-one (527.0 mg, 2.17 mM), 3-chlorobenzyl bromide (802.2 mg, 3.90 mM), a catalytic amount of sodium iodide (ca. 1 mg), and potassium carbonate (500.0 mg, 3.62 mM) was stirred at room temperature for 150 hours. The mixture was diluted with ethyl acetate, washed five times with H_2O, once with saturated brine, dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue was purified by column chromatography on silica gel (elution with gradient methylene chloride/ethyl acetate) to afford 537.1 mg (67%) of the 9-[(3-chlorophenyl)methyl]-5-carbomethoxy-1,2-dihydrocarbazol-4(3H)-one as a yellow foam. ^{1}H NMR ($CDCl_3$) δ 7.5-7.2 (m, 5H), 7.1 (s, 1H), 6.85 (m, 1H), 5.35 (s, 2H), 4.05 (s, 3H), 2.9 (t, 2H, J=6 Hz), 2.65 (t, 2H, J=6 Hz), and 2.3 (m , 2H). IR ($CHCl_3$, cm^{-1}) 3050, 2950, 1725, 1654, 1464, 1444, 1432, 1288 and 1120. MS (ES) m/e 366, 368, 370. Elemental Analyses for $C_{21}H_{18}NO_3Cl$:

Calculated: C, 68.57; H, 4.93; N, 3.81.

Found: C, 68.61; H, 4.92; N, 3.70.

B. 9-[(3-Chlorophenyl)methyl]-4-hydroxy-5-carbomethoxy carbazole

A solution of the 9-[(3-chlorophenyl)methyl]-5-carbomethoxy-1,2-dihydrocarbazol-4(3H)-one (480.5 mg, 1.31 mM) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (325.7 mg, 1.43 mM) in 50 mL of toluene was stirred between 70-80 °C for 3 hours. The mixture was purified directly by column chromatography on silica gel (elution with methylene chloride) to afford 172.6 mg (36%) of the 9-[(3-chlorophenyl)methyl]-4-hydroxy-5-carbomethoxy carbazole as a yellow foam. ^{1}H NMR ($CDCl_3$) δ 10.4 (s, 1H), 8.05 (d, 1H, J=8 Hz), 7.6 (d, 1H, J=8 Hz), 7.4 (m, 2H), 7.3-7.1 (m, 3H), 6.9-6.7 (m, 3H), 5.55 (s, 2H), and 4.15 (s, 3H). IR ($CHCl_3$, cm^{-1}) 3200 (br), 1684, 1598, 1442, 1428, 1331, 1285, and 1267. MS (ES) m/e 364, 366, 368.

Elemental Analyses for $C_{21}H_{16}NO_3Cl$:

Calculated: C, 68.95; H, 4.41; N, 3.83.

Found: C, 69.23; H, 4.52; N, 3.88.

C. 9-[(3-Chlorophenyl)methyl]-4-hydroxy-5-carbamoyl carbazole

A solution of the 9-[(3-chlorophenyl)methyl]-4-hydroxy-5-carbomethoxy carbazole (156.2 mg, 0.43 mM) in 5 mL THF and 20 mL concentrated aqueous ammonium hydroxide was sonicated for 5 hours at 40-50 °C. The mixture was diluted with ethyl acetate and acidified to pH 1 with 5 N HCl. The aqueous layer was extracted twice with ethyl acetate. The combined organic extracts were washed with saturated brine, dried over magnesium sulfate, filtered, and concentrated. The residue was purified by column chromatography on silica gel (elution with gradient methylene chloride/ethyl acetate) to afford 69.7 mg (47%) of the 9-[(3-chlorophenyl)methyl]-4-hydroxy-5-carbamoyl carbazole as a white solid. ^{1}H NMR

(DMSO-d6) δ 10.5 (s, 1H), 8.8 (br s, 1H), 8.4 (br s, 1H), 7.8 (dd, 1H, J=1 and 8 Hz), 7.45 (m, 2H), 7.3 (m, 3H), 7.2 (s, 1H), 7.1 (d, 1H, J=8 Hz), 6.95 (s, 1H), 6.6 (d, 1H, J=8 Hz), and 5.7 (s, 2H). IR ($CHCl_3$, cm^{-1}) 3433, 3202 (br), 1630, 1600, 1580, 1564, 1433, 1330, 1261, and 776. MS (ES) m/e 349, 351, 353.

Elemental Analyses for $C_{20}H_{15}N_2O_2Cl$:

Calculated: C, 68.48; H, 4.31; N, 7.99.

Found: C, 68.64; H, 4.55; N, 7.93.

D. {9-[(3-Chlorophenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, tert-butyl ester

40% Methanolic Triton B (0.053 mL, 0.12 mM) was added to a solution of the 9-[(3-chlorophenyl)methyl]-4-hydroxy-5-carbamoyl carbazole (33.2 mg, 0.12 mM) in 2 mL DMF at room temperature. After 3 minutes, t-butyl bromoacetate (53.8 mg, 0.27 mM) was added and the resultant mixture stirred at room temperature for 20 h. The mixture was diluted with ethyl acetate, washed four times with H_2O, once with saturated brine, dried over magnesium sulfate, filtered, and concentrated. The residue was purified by column chromatography on silica gel (elution with gradient methylene chloride/ethyl acetate) to afford 42.1 mg (95%) of the {9-[(3-chlorophenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, tert-butyl ester as a white solid. ^1H NMR (DMSO-d6) δ 7.6 (d, 1H, J=8 Hz), 7.5-6.8 (m, 10H), 6.55 (d, 1H, J=8 Hz), 5.7 (s, 2H), 4.8 (s, 2H), and 1.45 (s, 9H). IR ($CHCl_3$, cm^{-1}) 3450, 3400, 1744, 1676, 1591, 1457, 1369, and 1150. MS (FD) m/e 464, 466.

Elemental Analyses for $C_{26}H_{25}N_2O_4Cl$:

Calculated: C, 67.17; H, 5.42; N, 6.03.

Found: C, 67.17; H, 5.65; N, 5.97.

E. {9-[(3-Chlorophenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid

A solution of the {9-[(3-chlorophenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, tert-butyl ester (35.6 mg, 0.077 mM) in 2 mL of trifluoroacetic acid was stirred at room temperature for 6 hours. The solvent was removed *in vacuo*. The residue was triturated with ethyl acetate, then dried *in vacuo* to afford 31.4 mg (100%) of the {9-[(3-chlorophenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid as a white powder. ^{1}H NMR (DMSO-d6) δ 13.0 (br s, 1H), 7.75 (s, 1H), 7.6 (d, 1H, J=8 Hz), 7.4-7.25 (m, 7H), 7.2 (d, 1H, J=8 Hz), 7.0 (br t, 1H), 6.6 (d, 1H, J=8 Hz), 5.7 (s, 2H), and 4.8 (s, 2H). IR (KBr, cm^{-1}) 3456, 3416, 3335, 1735, 1638, 1617, 1580, 1499, 1452, 1431, 1431, 1329, 1255, 1157, 772, 764, and 717. MS (ES) m/e 407, 409, 411.

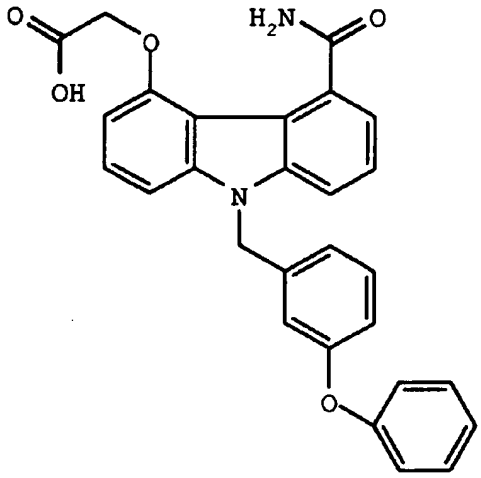
Elemental Analyses for $C_{22}H_{17}N_2O_4Cl$:

Calculated: C, 64.63; H, 4.19; N, 6.85.

Found: C, 64.55; H, 4.12; N, 6.74.

EXAMPLE 27

Preparation of {9-[(3-phenoxyphenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid



A. 9-[(3-Phenoxyphenyl)methyl]-5-carbomethoxy-1,2-dihydrocarbazol-4(3H)-one

40% Methanolic Triton B (1.53 mL, 3.4 mM) was slowly added dropwise to a solution of 5-carbomethoxy-1,2-dihydro-9H-carbazol-4(3H)-one (554.6 mg, 2.28 mM) in 5 mL of DMF at 25 °C. After 5 minutes, 3-phenoxybenzyl chloride (748.0 mg, 3.42 mM) was added and the resultant mixture stirred at room temperature for 24 hours. The mixture was diluted with ethyl acetate, washed three times with 1N HCl, three times with H_2O, once with saturated brine, dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue was purified by column chromatography on silica gel (elution with gradient methylene chloride/ethyl acetate) to afford 563.6 mg (58%) of 9-[(3-phenoxyphenyl)methyl]-5-carbomethoxy-1,2-dihydrocarbazol-4(3H)-one as a thick yellow oil. ^{1}H NMR (DMSO-d6) δ 7.7 (dd, 1H, J=1 and 8 Hz), 7.4-7.2 (m, 6H), 7.1 (t, 1H, J=8 Hz), 6.95 (m, 2H), 6.8-6.7 (m, 2H), 5.55 (s, 2H), 3.75 (s, 3H), 3.0 (t, 2H, J=6 Hz), 2.45 (t, 2H, J=6 Hz), and 2.1 (m , 2H). IR ($CHCl_3$, cm^{-1}) 3050, 2950, 1725, 1653, 1585, 1487, 1465, 1288, 1252, and 1119. MS (ES) m/e 426.

Elemental Analyses for $C_{27}H_{23}NO_4$:

Calculated: C, 76.22; H, 5.45; N, 3.29.

Found: C, 76.21; H, 5.35; N, 3.36.

B. 9-[(3-Phenoxyphenyl)methyl]-4-hydroxy-5-carbomethoxy carbazole

A solution of the 9-[(3-phenoxyphenyl)methyl]-5-carbomethoxy-1,2-dihydrocarbazol-4(3H)-one (544.5 mg, 1.28 mM) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (337.5 mg, 1.48 mM) in 20 mL of toluene was stirred between 70-80 °C for 4 hours. The mixture was purified directly by column chromatography on silica gel (elution with methylene chloride) to afford 107.0 mg (20%) of 9-[(3-

phenoxyphenyl)methyl]-4-hydroxy-5-carbomethyoxy carbazole as a yellow powder. ^{1}H NMR (DMSO-d6) δ 10.4 (s, 1H), 7.7 (d, 1H, J=8 Hz), 7.4-6.7 (m, 13H), 6.55 (d, 1H, J=8 Hz), 5.65 (s, 2H), and 3.85 (s, 3H). IR ($CHCl_3$, cm^{-1}) 3200 (br), 1687, 1597, 1584, 1487, 1441, 1332, 1284, 1267, and 1252. MS (ES) m/e 422, 424.

Elemental Analyses for $C_{27}H_{21}NO_4$:

Calculated: C, 76.58; H, 5.00; N, 3.31.

Found: C, 76.68; H, 5.20; N, 3.40.

c) 9-[(3-Phenoxyphenyl)methyl]-4-hydroxy-5-carbamoyl carbazole

A solution of the 9-[(3-phenoxyphenyl)methyl]-4-hydroxy-5-carbomethoxy carbazole (100.0 mg, 0.24 mM) in 5 mL THF and 20 mL concentrated aqueous ammonium hydroxide was sonicated for 24 hours at 40-50 °C. The mixture was diluted with ethyl acetate and acidified to pH 1 with 5 N HCl. The aqueous layer was extracted twice with ethyl acetate. The combined organic extracts were washed with saturated brine, dried over magnesium sulfate, filtered, and concentrated. The residue was purified by column chromatography on silica gel (elution with gradient methylene chloride/ethyl acetate) to afford 41.0 mg (43%) of the 9-[(3-phenoxyphenyl)methyl]-4-hydroxy-5-carbamoyl carbazole as a white solid. ^{1}H NMR (DMSO-d6) δ 10.5 (s, 1H), 8.8 (br s, 1H), 8.4 (br s, 1H), 7.8 (dd, 1H, J=1 and 8 Hz), 7.5-6.7 (m, 13H), 6.6 (d, 1H, J=8 Hz), and 5.7 (s, 2H). MS (ES) m/e 407, 409.

Elemental Analyses for $C_{26}H_{20}N_2O_3$:

Calculated: C, 76.46; H, 4.94; N, 6.86.

Found: C, 75.66; H, 5.29; N, 6.58.

D. {9-[(3-Phenoxyphenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, tert-butyl ester

40% Methanolic Triton B (0.054 mL, 0.12 mM) was added to a solution of the 9-[(3-phenoxyphenyl)methyl]-4-hydroxy-5-carbamoyl carbazole (39.5 mg, 0.10 mM) in 3 mL DMF at room temperature. After 3 minutes, t-butyl bromoacetate (54.8 mg, 0.27 mM) was added and the resultant mixture stirred at room temperature for 5 hours. The mixture was diluted with ethyl acetate, washed four times with H_2O, once with saturated brine, dried over magnesium sulfate, filtered, and concentrated. The residue was purified by column chromatography on silica gel (elution with gradient methylene chloride/ethyl acetate) to afford 33.0 mg (65%) of the {9-[(3-phenoxyphenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, tert-butyl ester as a white solid. ^{1}H NMR (DMSO-d6) δ 7.6 (d, 1H, J=8 Hz), 7.5-6.8 (m, 15H), 6.55 (d, 1H, J=8 Hz), 5.7 (s, 2H), 4.8 (s, 2H), and 1.45 (s, 9H). IR (KBr, cm^{-1}) 3450, 1748, 1670, 1582, 1486, 1246, 1225, and 1151. MS (ES) m/e 523.

Elemental Analyses for $C_{32}H_{30}N_2O_5$:

Calculated:	C, 73.55; H, 5.79; N, 5.36.
Found:	C, 73.84; H, 5.83; N, 5.30.

E. {9-[(3-Phenoxyphenyl)methyl]-5-carbamoylcarbazol-4-yl} oxyacetic acid

A solution of the {9-[(3-phenoxyphenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, tert-butyl ester (30.0 mg, 0.063 mM) in 2 mL of trifluoroacetic acid was stirred at room temperature for 6 hours. The solvent was removed *in vacuo*. The residue was dried *in vacuo* to afford 30.0 mg (100%) of the {9-[(3-phenoxyphenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid as a white powder. ^{1}H NMR (DMSO-d6) δ 13.0 (br s, 1H), 7.75 (s, 1H), 7.6 (d, 1H, J=8 Hz), 7.5-6.8 (m, 14H), 6.6 (d, 1H, J=8 Hz), 5.7 (s, 2H),

and 4.8 (s, 2H). IR (KBr, cm^{-1}) 3450, 3400, 1740, 1651, 1592, 1585, 1487, 1457, 1441, 1329, 1250, and 1158. MS (ES) m/e 465, 467.

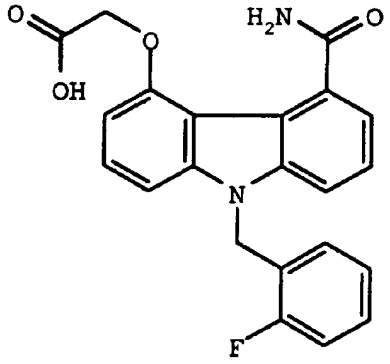
Elemental Analyses for $C_{28}H_{22}N_2O_5$:

Calculated: C, 72.09; H, 4.75; N, 6.00.

Found: C, 67.65; H, 4.64; N, 6.02.

EXAMPLE 28

Preparation of {9-[(2-Fluorophenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid



A. 9-[(2-Fluorophenyl)methyl]-5-carbomethoxy-1,2-dihydrocarbazol-4(3H)-one

40% Methanolic Triton B (2.82 mL, 6.2 mM) was slowly added dropwise to a solution of 5-carbomethoxy-1,2-dihydro-9H-carbazol-4(3H)-one (1.27 g, 5.22 mM) in 10 mL of DMF at 25 °C. After 5 minutes, 2-fluorobenzyl bromide (1.19 g, 6.2 mM) was added and the resultant mixture stirred at room temperature for 17 days. The mixture was diluted with ethyl acetate, washed five times with H_2O, once with saturated brine, dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue was purified by column chromatography on silica gel (elution with gradient methylene chloride/ethyl acetate) to afford 1.00 g (55%) of the 9-[(2-fluorophenyl)methyl]-5-carbomethoxy-1,2-dihydrocarbazol-4(3H)-one as a tan foam.

^{1}H NMR (DMSO-d6) δ 7.7 (dd, 1H, J=1 and 8 Hz), 7.4-7.2 (m, 4H), 7.1 (t, 1H, J=8 Hz), 6.7 (t, 1H, J=8 Hz), 5.65 (s, 2H), 3.8 (s, 3H), 3.0 (t, 2H, J=6 Hz), 2.45 (t, 2H, J=6 Hz), and 2.1 (m, 2H). IR ($CHCl_3$, cm^{-1}) 3050, 2950, 1725, 1652, 1464, 1441, 1288 and 1120. MS (ES)' m/e 350, 352.

Elemental Analyses for $C_{21}H_{18}NO_3F$:

Calculated: C, 71.78; H, 5.16; N, 3.99.

Found: C, 71.51; H, 5.08; N, 3.85.

B. 9-[(2-Fluorophenyl)methyl]-4-hydroxy-5-carbomethoxy carbazole

A solution of the 9-[(2-fluorophenyl)methyl]-5-carbomethoxy-1,2-dihydrocarbazol-4(3H)-one (1.00 g, 2.85 mM) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (800.0 mg, 3.51 mM) in 50 mL of toluene was stirred between 70-80 °C for 6 h. The mixture was purified directly by column chromatography on silica gel (elution with methylene chloride) to afford 250.0 mg (25%) of the 9-[(2-fluorophenyl)methyl]-4-hydroxy-5-carbomethyoxy carbazole as a dark solid. ^{1}H NMR (DMSO-d6) δ 10.2 (s, 1H), 7.7 (d, 1H, J=8 Hz), 7.4 (t, 1H, J=8 Hz), 7.3-6.85 (m, 6H), 6.75 (dt, 1H, J=.5 and 8 Hz), 6.6 (d, 1H, J=8 Hz), 5.7 (s, 2H), and 3.85 (s, 3H). IR ($CHCl_3$, cm^{-1}) 3200 (br), 1686, 1598, 1490, 1442, 1285, 1268, 1230, and 1139. MS (ES) m/e 348, 350.

Elemental Analyses for $C_{21}H_{16}NO_3F$:

Calculated: C, 72.20; H, 4.62; N, 4.01.

Found: C, 71.32; H, 4.75; N, 4.11.

C. 9-[(2-Fluorophenyl)methyl]-4-hydroxy-5-carbamoyl carbazole

A solution of the 9-[(2-fluorophenyl)methyl]-4-hydroxy-5-carbomethoxy carbazole (237.5 mg, 0.68 mM) in 10 mL THF and 40 mL concentrated aqueous ammonium hydroxide was sonicated for 20 h at 40-50 °C. The mixture was diluted with

ethyl acetate and acidified to pH 1 with 5 N HCl. The aqueous layer was extracted twice with ethyl acetate. The combined organic extracts were washed with saturated brine, dried over magnesium sulfate, filtered, and concentrated. The residue was purified by column chromatography on silica gel (elution with gradient methylene chloride/ethyl acetate) to afford 89.7 mg (40%) of the 9-[(2-fluorophenyl)methyl]-4-hydroxy-5-carbamoyl carbazole as a white solid. ^{1}H NMR (DMSO-d6) δ 10.5 (s, 1H), 8.8 (br s, 1H), 8.4 (br s, 1H), 7.8 (dd, 1H, J=1 and 8 Hz), 7.5-6.9 (m, 7H), 6.65 (m, 2H), and 5.75 (s, 2H). IR (KBr, cm^{-1}) 3395, 3192 (br), 1621, 1599, 1580, 1564, 1491, 1455, 1334, 1261, and 774. MS (ES) m/e 333, 335.

Elemental Analyses for $C_{20}H_{15}N_2O_2F$:

Calculated: C, 71.85; H, 4.52; N, 8.38.

Found: C, 72.57; H, 4.88; N, 7.84.

D. {9-[(2-Fluorophenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, methyl ester

40% Methanolic Triton B (0.14 mL, 0.31 mM) was added to a solution of the 9-[(2-fluorophenyl)methyl]-4-hydroxy-5-carbamoyl carbazole (51.9 mg, 0.155 mM) in 5 mL DMF at room temperature. After 3 minutes, methyl bromoacetate (110.5 mg, 0.72 mM) was added and the resultant mixture stirred at room temperature for 20 hours. The mixture was diluted with ethyl acetate, washed four times with H_2O, once with saturated brine, dried over magnesium sulfate, filtered, and concentrated. The residue was purified by column chromatography on silica gel (elution with gradient methylene chloride/ethyl acetate) to afford 72.8 mg (71%) of the {9-[(2-fluorophenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, methyl ester as a white solid. ^{1}H NMR (DMSO-d6) δ 7.65 (d, 1H, J=8 Hz), 7.5 (s, 1H), 7.4-7.2 (m, 5H), 7.15 (s, 1H), 7.1 (d, 1H, J=8 Hz), 7.05 (t, 1H, J=8

Hz), 6.7 (t, 1H, J=8 Hz), 6.55 (d, 1H, J=8 Hz), 5.7 (s, 2H), 4.85 (s, 2H), and 3.7 (s, 3H). IR ($CHCl_3$, cm^{-1}) 3436, 1763, 1675,1457, 1327, 1208, 1198, 1150, 1102, 772, 756, and 719. MS (FD) m/e 407.

Elemental Analyses for $C_{23}H_{19}N_2O_4F$:

Calculated: C, 67.97; H, 4.71; N, 6.89.

Found: C, 68.00; H, 4.92; N, 6.75.

E. {9-[(2-Fluorophenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid

A solution of the {9-[(2-fluorophenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, methyl ester (47.9 mg, 0.118 mM) and 0.28 mL (0.28 mM) of 1 N NaOH in 10 mL of methanol was sonicated for 6 hours at 50-60 °C, then stirred at room temperature for 16 hours. The mixture was diluted with ethyl acetate and acidified to pH 1 with 5 N HCl. The aqueous layer was extracted twice with ethyl acetate. The combined organic extracts were washed with saturated brine, dried over magnesium sulfate, filtered, and concentrated to afford 42.8 mg (92%) of the {9-[(2-fluorophenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid as a white powder. ^1H NMR (DMSO-d6) δ 7.75 (s, 1H), 7.6 (d, 1H, J=8 Hz), 7.5-7.25 (m, 6H), 7.15 (d, 1H, J=8 Hz), 7.05 (dt, 1H, J=1 and 8 Hz), 6.75 (dt, 1H, J=1 and 8 Hz), , 6.65 (d, 1H, J=8 Hz), 5.7 (s, 2H), and 4.8 (s, 2H). IR (KBr, cm^{-1}) 3428, 3400, 1737, 1635, 1617, 1583, 1572, 1500, 1491, 1453, 1434, 1330, 1248, 1158, 1098, 760, and 714. MS (FD) m/e 392.

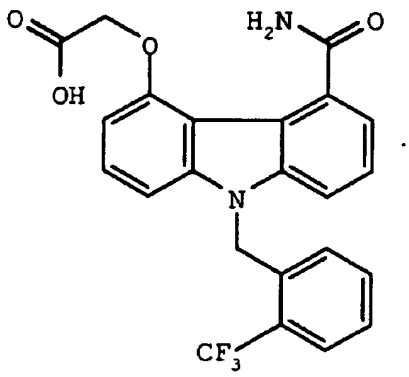
Elemental Analyses for $C_{22}H_{17}N_2O_4F$:

Calculated: C, 67.34; H, 4.37; N, 7.14.

Found: C, 66.65; H, 4.55; N, 6.92.

EXAMPLE 29

Preparation of {9-[(2-trifluoromethylphenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid



A. 9-[(2-Trifluoromethylphenyl)methyl]-5-carbomethoxy-1,2-dihydrocarbazol-4(3H)-one

40% Methanolic Triton B (2.18 mL, 4.8 mM) was slowly added dropwise to a solution of 5-carbomethoxy-1,2-dihydro-9H-carbazol-4(3H)-one (973 mg, 4.0 mM) in 10 mL of DMF at -10 °C. After 30 minutes, 2-(trifluoromethyl)benzyl bromide (1.3 g, 5.2 mM) was added and the resultant mixture stirred at room temperature for 23 hours. The mixture was diluted with ethyl acetate, washed five times with H_2O, once with saturated brine, dried over anhydrous magnesium sulfate, filtered, concentrated, and dried *in vacuo* to afford 1.34 g (83%) of the 9-[(2-trifluoromethylphenyl)methyl]-5-carbomethoxy-1,2-dihydrocarbazol-4(3H)-one as a tan solid. ^{1}H NMR ($CDCl_3$) δ 7.7 (d, 1H, J=8 Hz), 7.4-7.1 (m, 5H), 6.4 (d, 1H, J=8 Hz), 5.5 (s, 2H), 4.05 (s, 3H), 2.8 (t, 2H, J=6 Hz), 2.6 (t, 2H, J=6 Hz), and 2.2 (m, 2H). IR (KBr, cm^{-1}) 1729 and 1656. MS (ES) m/e 402.

Elemental Analyses for $C_{22}H_{18}NO_3F_3$:

Calculated:	C, 65.83; H, 4.52; N, 3.49; F, 14.20.
Found:	C, 66.07; H, 4.59; N, 3.20; F, 13.95.

B. 9-[(2-Trifluoromethylphenyl)methyl]-4-hydroxy-5-carbomethoxy carbazole

A solution of the 9-[(2-trifluoromethylphenyl)methyl]-5-carbomethoxy-1,2-dihydrocarbazol-4(3H)-one (1.21 g, 3.00 mM) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (764 mg, 3.3 mM) in 25 mL of toluene was stirred between 80-90 °C for 7 h. The mixture was purified directly by column chromatography on silica gel (elution with methylene chloride) to afford 340.0 mg (28%) of the 9-[(2-trifluoromethylphenyl)methyl]-4-hydroxy-5-carbomethyoxy carbazole as a brown powder. ^{1}H NMR ($CDCl_3$) δ 10.4 (s, 1H), 8.0 (d, 1H, J=8 Hz), 7.7 (d, 1H, J=8 Hz), 7.5-7.2 (m, 5H), 6.85 (m, 2H), 6.45 (d, 1H, J=8 Hz), 5.7 (s, 2H), and 4.1 (s, 3H). IR ($CHCl_3$, cm^{-1}) 3200 (br) and 1677. MS (ES) m/e 398, 400.

Elemental Analyses for $C_{22}H_{16}NO_3F_3$:

Calculated:	C, 66.17; H, 4.04; N, 3.51; F, 14.27.
Found:	C, 66.93; H, 4.06; N, 3.54; F, 14.00.

C. 9-[(2-Trifluoromethylphenyl)methyl]-4-hydroxy-5-carbamoyl carbazole

A solution of the 9-[(2-trifluoromethylphenyl)methyl]-4-hydroxy-5-carbomethoxy carbazole (310 mg, 0.77 mM) in 5 mL THF and 20 mL concentrated aqueous ammonium hydroxide was sonicated for 25 hours at 40-50 °C. The mixture was diluted with ethyl acetate and acidified to pH 1 with 5 N HCl. The aqueous layer was extracted twice with ethyl acetate. The combined organic extracts were washed with saturated brine, dried over magnesium sulfate, filtered, and concentrated. The residue was purified by column chromatography on silica gel (elution with gradient methylene chloride/ethyl acetate) to afford 145 mg (49%) of the 9-[(2-trifluoromethylphenyl)methyl]-4-hydroxy-5-carbamoyl

carbazole as a white solid. ^{1}H NMR (DMSO-d6) δ 10.5 (s, 1H), 8.8 (br s, 1H), 8.4 (br s, 1H), 7.8 (d, 1H, J=8 Hz), 7.6-7.2 (m, 6H), 6.85 (d, 1H, J=8 Hz), 6.6 (d, 1H, J=8 Hz), 6.25 (d, 1H, J=8 Hz), and 5.8 (s, 2H). IR (KBr, cm^{-1}) 3460, 3360, and 1589. MS (ES) m/e 383, 385.

Elemental Analyses for $C_{21}H_{15}N_2O_2F_3$:

Calculated: C, 65.62; H, 3.93; N, 7.29; F, 14.83.

Found: C, 65.65; H, 3.94; N, 7.51; F, 14.94.

D. {9-[(2-Trifluoromethylphenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, methyl ester

40% Methanolic Triton B (0.18 mL, 0.4 mM) was added to a solution of the 9-[(2-trifluoromethylphenyl)methyl]-4-hydroxy-5-carbamoyl carbazole (120 mg, 0.31 mM) in 5 mL DMF at room temperature. After 15 minutes, methyl bromoacetate (98.5 mg, 0.62 mM) was added and the resultant mixture stirred at room temperature for 4.5 hours. The mixture was diluted with ethyl acetate, washed four times with H_2O, 1 N HCl, H_2O, sat. $NaHCO_3$, and saturated brine, dried over magnesium sulfate, filtered, and concentrated. The residue was purified by column chromatography on silica gel (elution with gradient methylene chloride/ethyl acetate/THF) to afford 95 mg (67%) of the {9-[(2-trifluoromethylphenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, methyl ester as a white solid. ^{1}H NMR ($CDCl_3$) δ 7.7 (d, 1H, J=8 Hz), 7.5-7.2 (m, 6H), 6.95 (d, 1H, J=8 Hz), 6.6 (d, 1H, J=8 Hz), 6.45 (d, 1H, J=8 Hz), 6.3 (br s, 1H), 6.1 (br s, 1H), 5.7 (s, 2H), 4.9 (s, 2H), and 3.9 (s, 3H). IR ($CHCl_3$, cm^{-1}) 1763 and 1674. MS (ES) m/e 457.

Elemental Analyses for $C_{24}H_{19}N_2O_4F_3$:

Calculated: C, 63.16; H, 4.20; N, 6.14.

Found: C, 61.82; H, 4.31; N, 5.86.

E. {9-[(2-Trifluoromethylphenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid

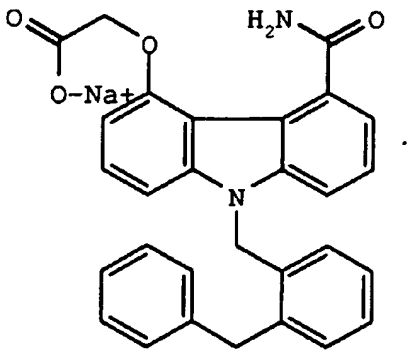
A solution of the {9-[(2-trifluoromethylphenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, methyl ester (70 mg, 0.153 mM) and 0.21 mL (0.21 mM) of 1 N NaOH in 5 mL of methanol was sonicated for 23 hours at 50-60 °C. The methanol was removed *in vacuo* and the mixture acidified to pH 1.6 with 1 N HCl. The resultant white precipitate was collected by filtration, washed with H_2O, small amounts of MeOH and diethyl ether, then dried *in vacuo* to afford 59 mg (88%) of the {9-[(2-trifluoromethylphenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid as a white powder. ^1H NMR (DMSO-d6) δ 13.0 (br s, 1H), 7.8 (d, 1H, J=8 Hz), 7.75 (s, 1H), 7.5-7.3 (m, 6H), 7.1 (d, 1H, J=8 Hz), 7.05 (d, 1H, J=8 Hz), 6.6 (d, 1H, J=8 Hz), , 6.3 (d, 1H, J=8 Hz), 5.8 (s, 2H), and 4.8 (s, 2H). IR (KBr, cm^{-1}) 1737 and 1635. MS (ES) m/e 441, 443.

Elemental Analyses for $C_{23}H_{17}N_2O_4F_3$:

Calculated:	C, 62.45;	H, 3.87; N, 6.33; F, 12.88.
Found:	C, 60.86;	H, 3.89; N, 6.08; F, 12.59.

EXAMPLE 30

Preparation of {9-[(2-benzylphenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, sodium salt



A. 2-Benzylbenzyl bromide

A solution of phosphorus tribromide (2.1 mL, 6.0 g, 22.1 mM) in 30 mL of carbon tetrachloride was slowly added dropwise to solution of 2-benzylbenzyl alcohol (1.98 g, 10 mM) in 70 mL of carbon tetrachloride at 0 °C. The mixture was stirred at 0 °C for 2 hours, then at room temperature for 2 hours. The solvent was removed *in vacuo* and the residue diluted with ethyl acetate and saturated aqueous sodium bicarbonate. The organic layer was washed with brine, dried over magnesium sulfate, filtered, and concentrated to afford 2.6 g (99%)of 2-benzylbenzyl bromide as a yellow solid. ^{1}H NMR (DMSO-d6) δ 7.5-7.0 (m, 9H), 4.7 (s, 2H), and 4.15 (s, 2H). IR ($CHCl_3$, cm^{-1}) 3065, 1601, 1495,and 1453. MS (FD) m/e 260, 262.

Elemental Analyses for $C_{14}H_{13}Br$:

Calculated: C, 64.37; H, 4.98; N, 0.00.

Found: C, 65.26; H, 5.26; N, 0.00.

B. 9-[(2-Benzylphenyl)methyl]-5-carbomethoxy-1,2-dihydrocarbazol-4(3H)-one

40% Methanolic Triton B (0.95 mL, 2.1 mM) was slowly added dropwise to a solution of 5-carbomethoxy-1,2-dihydro-9H-carbazol-4(3H)-one (510 mg, 2.1 mM) in 30 mL of DMF at -10 °C. After 3 minutes, 2-benzylbenzyl bromide (548 mg, 2.1 mM) was added and the resultant mixture stirred at room temperature for 6 hours. The mixture was diluted with ethyl acetate and 1 N HCl, washed twice with H_2O, once with saturated brine, dried over anhydrous magnesium sulfate, filtered, concentrated, and dried *in vacuo*. The reside was purified by column chromatography on silica gel (elution with ethyl acetate) to afford 324 mg (36%) of the 9-[(2-benzylphenyl)methyl]-5-carbomethoxy-1,2-dihydrocarbazol-4(3H)-one as a tan solid. ^{1}H NMR ($CDCl_3$) δ 7.45-7.0 (m, 10H), 6.9 (d, 1H, J=8 Hz), 6.3 (d, 1H, J=8 Hz), 5.2 (s, 2H), 4.15 (s, 2H), 4.05 (s, 3H), 2.5 (m, 4H), and 2.1 (m , 2H). IR (KBr, cm^{-1}) 1726, 1653, 1466, 1443, 1411, 1283, 1200, 1119, and 749. MS (ES) m/e 422, 424.

Elemental Analyses for $C_{28}H_{25}NO_3$:

Calculated:	C, 79.43; H, 5.91; N, 3.31.
Found:	C, 79.58; H, 5.94; N, 3.32.

C. 9-[(2-Benzylphenyl)methyl]-4-hydroxy-5-carbomethoxy carbazole

A solution of the 9-[(2-benzylphenyl)methyl]-5-carbomethoxy-1,2-dihydrocarbazol-4(3H)-one (480 mg, 1.14 mM) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (250 mg, 5.0 mM) in 30 mL of toluene was stirred between 80-90 °C for 5 hours. The mixture was purified directly by column chromatography on silica gel (elution with methylene chloride/ethyl acetate) to afford 166 mg (35%) of the 9-[(2-benzylphenyl)methyl]-4-hydroxy-5-carbomethyoxy carbazole as

a yellow solid. ^{1}H NMR ($CDCl_3$) δ 10.4 (s, 1H), 8.0 (d, 1H, J=8 Hz), 7.4-7.0 (m, 11H), 6.8 (d, 1H, J=8 Hz), 6.6 (d, 1H, J=8 Hz), 6.4 (d, 1H, J=8 Hz), 5.4 (s, 2H), 4.25 (s, 2H), and 4.1 (s, 3H). IR ($CHCl_3$, cm^{-1}) 1684, 1597, 1495, 1452, 1442, 1333, 1284, 1269, and 1140. MS (ES) m/e 420, 422.

D. 9-[(2-Benzylphenyl)methyl]-4-hydroxy-5-carbamoyl carbazole

A solution of the 9-[(2-benzylphenyl)methyl]-4-hydroxy-5-carbomethoxy carbazole (166 mg, 0.39 mM) in 8 mL THF and 30 mL concentrated aqueous ammonium hydroxide was sonicated for 30 hours at 40-50 °C. The mixture was diluted with ethyl acetate and acidified to pH 1 with 5 N HCl. The aqueous layer was extracted twice with ethyl acetate. The combined organic extracts were washed with saturated brine, dried over magnesium sulfate, filtered, and concentrated. The residue was purified by column chromatography on silica gel (elution with ethyl acetate) to afford 70 mg (44%) of the 9-[(2-benzylphenyl)methyl]-4-hydroxy-5-carbamoyl carbazole as a white solid. ^{1}H NMR ($CDCl_3$) δ 8.0 (d, 1H, J=8 Hz), 7.4-7.0 (m, 12H), 6.8 (d, 1H, J=8 Hz), 6.6 (d, 1H, J=8 Hz), 6.5 (m, 1H), 6.4 (m, 1H), 5.8 (s, 1H), 5.4 (s, 2H), and 4.2 (s, 2H). MS (ES) m/e 405, 407.

E. {9-[(2-Benzylphenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, methyl ester

40% Methanolic Triton B (0.12 mL, 0.26 mM) was added to a solution of the 9-[(2-benzylphenyl)methyl]-4-hydroxy-5-carbamoyl carbazole (70 mg, 0.17 mM) in 10 mL DMF at 25 °C. After 3 minutes, methyl bromoacetate (55 mg, 0.34 mM) was added and the resultant mixture stirred at room temperature for 25 hours. The mixture was diluted with ethyl acetate,

washed with 1 N HCl, H_2O, and saturated brine, dried over magnesium sulfate, filtered, and concentrated. The residue was purified by column chromatography on silica gel (elution with ethyl acetate) to afford 60 mg (73%) of the {9-[(2-benzylphenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, methyl ester as a white solid. ^{1}H NMR ($CDCl_3$) δ 7.4-7.00 (m, 14H), 6.65 (d, 1H, J=8 Hz), 6.55 (d, 1H, J=8 Hz), 6.4 (d, 1H, J=8 Hz), 5.4 (s, 2H), 4.95 (s, 2H), 4.2 (s, 2H), and 3.80 (s, 3H). IR (KBr, cm^{-1}) 3414, 3186, 1759, 1625, 1583, 1500, 1452, 1424, 1340, 1325, 1213, 1199, and 1108. MS (ES) m/e 477, 479.

Elemental Analyses for $C_{30}H_{26}N_2O_4$:

Calculated:	C, 75.31; H, 5.44; N, 5.86.
Found:	C, 75.08; H, 5.61; N, 5.70.

F. {9-[(2-Benzylphenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, sodium salt.

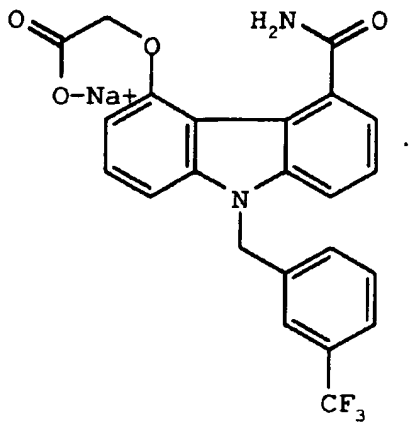
A solution of the {9-[(2-benzylphenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, methyl ester (16.2 mg, 0.034 mM) and 0.034 mL (0.034 mM) of 1 N NaOH in 3 mL of ethanol was stirred for 16 hours at 25 °C. The resultant white precipitate was collected by filtration, washed with a small amount of EtOH, then dried *in vacuo* to afford 7.1 mg (70%) of the {9-[(2-benzylphenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, sodium salt as a white powder. ^{1}H NMR (DMSO-d6) δ 7.5-6.8 (m, 14H), 6.65 (d, 1H, J=8 Hz), 6.55 (d, 1H, J=8 Hz), 6.05 (d, 1H, J=8 Hz), 5.55 (s, 2H), 4.35 (s, 2H), and 4.3 (s, 2H). IR ($CHCl_3$, cm^{-1}) 1666, 1616, 1495, 1452, and 1422. MS (ES) m/e 463, 465.

Elemental Analyses for $C_{29}H_{23}N_2O_4Na$:

Calculated:	C, 71.60; H, 4.73; N, 5.76.
Found:	C, 64.68; H, 4.79; N, 5.08.

EXAMPLE 31

Preparation of {9-[(3-trifluoromethylphenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, sodium salt



A. 9-[(3-Trifluoromethylphenyl)methyl]-5-carbomethoxy-1,2-dihydrocarbazol-4(3H)-one

40% Methanolic Triton B (2.18 mL, 4.8 mM) was slowly added dropwise to a solution of 5-carbomethoxy-1,2-dihydro-9H-carbazol-4(3H)-one (973 mg, 4.0 mM) in 10 mL of DMF at -10 °C. After 30 minutes, 3-(trifluoromethyl)benzyl chloride (1.53 g, 6.0 mM) and sodium iodide (900 mg, 6.0 mM) were added and the resultant mixture stirred at room temperature for 25 hours. The mixture was diluted with ethyl acetate, washed five times with H_2O, 1 N HCl, H_2O, sat $NaHCO_3$, and saturated brine, dried over anhydrous magnesium sulfate, filtered, concentrated, and dried *in vacuo*. The residue was purified by column chromatography on silica gel (elution with gradient methylene chloride/ethyl acetate) to afford 1.02 g (63%) of the 9-[(3-trifluoromethylphenyl)methyl]-5-carbomethoxy -1,2-dihydrocarbazol-4(3H)-one as a tan solid. ^1H NMR ($CDCl_3$) δ 7.6 (d, 1H, J=8 Hz), 7.45-7.2 (m, 5H), 7.0 (d, 1H, J=8 Hz), 5.4 (s, 2H), 4.05 (s, 3H), 2.85 (t, 2H, J=6 Hz), 2.6 (t, 2H, J=6 Hz), and 2.2 (m, 2H). IR (KBr, cm^{-1}) 1727 and 1652. MS (ES) m/e 400, 402.

Elemental Analyses for $C_{22}H_{18}NO_3F_3$:

Calculated: C, 65.83; H, 4.52; N, 3.49; F, 14.20.

Found: C, 65.63; H, 4.58; N, 3.39; F, 14.14.

B. 9-[(3-Trifluoromethylphenyl)methyl]-4-hydroxy-5-carbomethoxy carbazole

A solution of the 9-[(3-trifluoromethylphenyl)methyl]-5-carbomethoxy-1,2-dihydrocarbazol-4(3H)-one (1.21 g, 3.00 mM) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (764 mg, 3.3 mM) in 25 mL of toluene was stirred between 80-90 °C for 7 hours. The mixture was purified directly by column chromatography on silica gel (elution with methylene chloride) to afford 340.0 mg (28%) of the 9-[(3-trifluoromethylphenyl)methyl]-4-hydroxy-5-carbomethyoxy carbazole as a yellow solid. ^{1}H NMR ($CDCl_3$) δ 10.35 (s, 1H), 8.0 (d, 1H, J=8 Hz), 7.6-7.3 (m, 6H), 7.05 (d, 1H, J=8 Hz), 6.85 (m, 2H), 5.6 (s, 2H), and 4.1 (s, 3H). IR ($CHCl_3$, cm^{-1}) 3378 and 1712. MS (ES) m/e 398, 400.

Elemental Analyses for $C_{22}H_{16}NO_3F_3$:

Calculated: C, 66.17; H, 4.04; N, 3.51.

Found: C, 66.99; H, 4.12; N, 3.53; F.

C. 9-[(3-Trifluoromethylphenyl)methyl]-4-hydroxy-5-carbamoyl carbazole

A solution of the 9-[(3-trifluoromethylphenyl)methyl]-4-hydroxy-5-carbomethoxy carbazole (250 mg, 0.625 mM) in 5 mL THF and 20 mL concentrated aqueous ammonium hydroxide was sonicated for 30 h at 40-50 °C. The mixture was diluted with ethyl acetate and acidified to pH 1 with 5 N HCl. The aqueous layer was extracted three times with ethyl acetate. The combined organic extracts were washed with saturated brine, dried over magnesium sulfate, filtered, and concentrated. The residue was purified by column

chromatography on silica gel (elution with gradient methylene chloride/ethyl acetate) to afford 120 mg (50%) of the 9-[(3-trifluoromethylphenyl)methyl]-4-hydroxy-5-carbamoyl carbazole as a white solid. ^{1}H NMR (DMSO-d6) δ 10.5 (s, 1H), 8.8 (br s, 1H), 8.4 (br s, 1H), 7.8 (d, 1H, J=8 Hz), 7.6-7.5 (m, 5H), 7.3 (t, 1H, J=8 Hz), 7.15 (d, 1H, J=8 Hz), 7.1 (d, 1H, J=8 Hz), 6.6 (d, 1H, J=8 Hz), and 5.8 (s, 2H). IR (KBr, cm^{-1}) 3429, 3206, and 1630. MS (ES) m/e 383, 385.

Elemental Analyses for $C_{21}H_{15}N_2O_2F_3$:

Calculated: C, 65.62; H, 3.93; N, 7.29.

Found: C, 67.50; H, 4.00; N, 7.19.

D. {9-[(3-Trifluoromethylphenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, methyl ester

40% Methanolic Triton B (0.18 mL, 0.4 mM) was added to a solution of the 9-[(3-trifluoromethylphenyl)methyl]-4-hydroxy-5-carbamoyl carbazole (115 mg, 0.3 mM) in 5 mL DMF at room temperature. After 15 minutes, methyl bromoacetate (95 mg, 0.6 mM) was added and the resultant mixture stirred at room temperature for 22 hours. The mixture was diluted with ethyl acetate, washed four times with H_2O, 1 N HCl, H_2O, sat. $NaHCO_3$, and saturated brine, dried over magnesium sulfate, filtered, and concentrated. The residue was purified by column chromatography on silica gel (elution with ethyl acetate) to afford 120 mg (88%) of the {9-[(3-trifluoromethylphenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, methyl ester as a white solid. ^{1}H NMR ($CDCl_3$) δ 7.5-7.2 (m, 7H), 7.1 (d, 1H, J=8 Hz), 7.0 (d, 1H, J=8 Hz), 6.6 (d, 1H, J=8 Hz), 6.4 (br s, 1H), 6.0 (br s, 1H), 5.55 (s, 2H), 4.9 (s, 2H), and 3.9 (s, 3H). IR (KBr, cm^{-1}) 1763 and 1673. MS (ES) m/e 457.

Elemental Analyses for $C_{24}H_{19}N_2O_4F_3$:

Calculated: C, 63.16; H, 4.20; N, 6.14.
Found: C, 61.37; H, 4.19; N, 5.77.

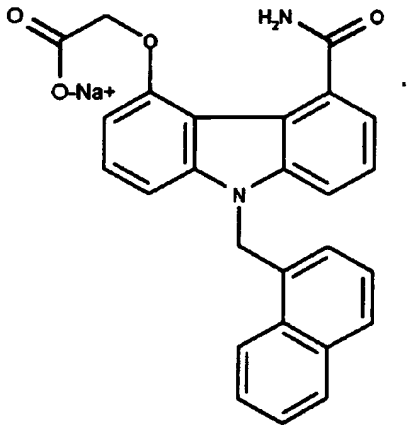
E. {9-[(3-Trifluoromethylphenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, sodium salt.

A solution of the {9-[(3-trifluoromethylphenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, methyl ester (91 mg, 0.153 mM) and 0.22 mL (0.22 mM) of 1 N NaOH in 8 mL of ethanol was stirred for 17 h at 25 °C. The ethanol was removed *in vacuo*. The resultant white precipitate was collected by filtration, washed with small amounts of EtOH and diethyl ether, then dried *in vacuo* to afford 75 mg (81%) of the {9-[(3-trifluoromethylphenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, sodium salt as a white powder. ^{1}H NMR (DMSO-d6) δ 7.65 (s, 1H), 7.6 (m, 4H), 7.45 (t, 1H, J=8 Hz), 7.35 (t, 1H, J=8 Hz), 7.3 (t, 1H, J=8 Hz), 7.2 (d, 1H, J=8 Hz), 7.1 (d, 1H, J=8 Hz), 7.05 (d, 1H, J=8 Hz), 6.5 (d, 1H, J=8 Hz), 5.75 (s, 2H), and 4.3 (s, 2H). IR (KBr, cm^{-1}) 1665 and 1618. MS (ES) m/e 441, 443.

Elemental Analyses for $C_{23}H_{16}N_2O_4F_3Na$:
Calculated: C, 59.49; H, 3.47; N, 6.03.
Found: C, 60.69; H, 3.78; N, 5.75.

EXAMPLE 32

Preparation of {9-[(1-naphthyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, sodium salt



A. 9-[(1-Naphthyl)methyl]-5-carbomethoxy-1,2-dihydrocarbazol-4(3H)-one

40% Methanolic Triton B (1.6 mL, 3.6 mM) was slowly added dropwise to a solution of 5-carbomethoxy-1,2-dihydro-9H-carbazol-4(3H)-one (870 mg, 3.6 mM) in 30 mL of DMF at 25 °C. After 5 minutes, 1-chloromethyl naphthylene (642 mg, 3.6 mM) and sodium iodide (450 mg, 3.0 mM) were added and the resultant mixture stirred at room temperature for 25 hours. The mixture was diluted with ethyl acetate, washed five times with H_2O, 1 N HCl, H_2O, sat $NaHCO_3$, and saturated brine, dried over anhydrous magnesium sulfate, filtered, concentrated, and dried *in vacuo*. The residue was purified by column chromatography on silica gel (elution with ethyl acetate) to afford 560 mg (41%) of the 9-[(1-naphthyl)methyl]-5-carbomethoxy-1,2-dihydrocarbazol-4(3H)-one as a yellow solid. ^1H NMR ($CDCl_3$) δ 8.0 (d, 1H, J=8 Hz), 7.9 (d, 1H, J=8 Hz), 7.7 (d, 1H, J=8 Hz), 7.6 (t, 1H, J=8 Hz), 7.55 (t, 1H, J=8 Hz), 7.35 (d, 1H, J=8 Hz), 7.15-7.05 (m, 3H), 6.4 (d, 1H, J=8 Hz), 5.8 (s, 2H), 4.05 (s,

3H), 2.8 (t, 2H, J=6 Hz), 2.55 (t, 2H, J=6 Hz), and 2.2 (m , 2H). IR (KBr, cm^{-1}) 1721, 1646, 1464, 1448, 1438, 1285, 1122, 796, and 761. MS (ES) m/e 382, 384.

Elemental Analyses for $C_{25}H_{21}NO_3$:

Calculated: C, 78.33; H, 5.48; N, 3.66

Found: C, 76.28; H, 5.46; N, 3.93.

B. 9-[(1-Naphthyl)methyl]-4-hydroxy-5-carbomethoxy carbazole

A solution of the 9-[(1-naphthyl)methyl]-5-carbomethoxy-1,2-dihydrocarbazol-4(3H)-one (540 mg, 1.4 mM) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (304 mg, 1.33 mM) in 30 mL of toluene was stirred between 80-90 °C for 5 hours. The mixture was purified directly by column chromatography on silica gel (elution with ethyl acetate) to afford 240.0 mg (45%) of the 9-[(1-naphthyl)methyl]-4-hydroxy-5-carbomethyoxy carbazole as a yellow solid. ^1H NMR (DMSO-d6) δ 10.25 (s, 1H), 8.35 (d, 1H, J=8 Hz), 8.0 (d, 1H, J=8 Hz), 7.8 (d, 1H, J=8 Hz), 7.6-7.1 (m, 7H), 6.9 (d, 1H, J=8 Hz), 6.6 (d, 1H, J=8 Hz), 6.3 (d, 1H, J=8 Hz), 6.15 (s, 2H), and 3.8 (s, 3H). IR ($CHCl_3$, cm^{-1}) 1685, 1598, 1442, 1269, and 1140. MS (ES) m/e 380, 382.

Elemental Analyses for $C_{25}H_{19}NO_3$:

Calculated: C, 78.74; H, 4.99; N, 3.67.

Found C, 78.67; H, 5.14; N, 3.54.

C. 9-[(1-Naphthyl)methyl]-4-hydroxy-5-carbamoyl carbazole

A solution of the 9-[(1-naphthyl)methyl]-4-hydroxy-5-carbomethoxy carbazole (210 mg, 0.55 mM) in 10 mL THF and 30 mL concentrated aqueous ammonium hydroxide was sonicated for 20 hours at 40-50 °C. The mixture was diluted with ethyl acetate and acidified to pH 1 with 5 N HCl. The aqueous

layer was extracted three times with ethyl acetate. The combined organic extracts were washed with saturated brine, dried over magnesium sulfate, filtered, and concentrated. The residue was purified by column chromatography on silica gel (elution with gradient hexanes/ethyl acetate) to afford 80 mg (40%) of the 9-[(1-naphthyl)methyl]-4-hydroxy-5-carbamoyl carbazole as a white solid. ^{1}H NMR (DMSO-d6) δ 10.55 (s, 1H), 8.8 (br s, 1H), 8.4 (br s, 1H), 8.35 (d, 1H, J=8 Hz), 7.95 (d, 1H, J=8 Hz), 7.8 (d, 1H, J=8 Hz), 7.65 (m, 4H), 7.45 (m, 2H), 7.25 (t, 1H, J=8 Hz), 7.15 (t, 1H, J=8 Hz), 6.9 (d, 1H, J=8 Hz), 6.6 (d, 1H, J=8 Hz), and 6.2 (s, 2H). MS (ES) m/e 365, 367.

D. {9-[(1-Naphthyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, methyl ester

40% Methanolic Triton B (0.2 mL, 0.26 mM) was added to a solution of the 9-[(1-naphthyl)methyl]-4-hydroxy-5-carbamoyl carbazole (80 mg, 0.22 mM) in 7 mL DMF at room temperature. After 15 minutes, methyl bromoacetate (40 mg, 0.3 mM) was added and the resultant mixture stirred at room temperature for 3 hours. The mixture was diluted with ethyl acetate, washed twice with H_2O, and once with saturated brine, dried over magnesium sulfate, filtered, and concentrated. The residue was purified by column chromatography on silica gel (elution with ethyl acetate) to afford 81 mg (85%) of the {9-[(1-naphthyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, methyl ester as a white solid. ^{1}H NMR ($CDCl_3$) δ 8.2 (d, 1H, J=8 Hz), 8.05 (d, 1H, J=8 Hz), 7.85-7.0 (m, 11H), 6.65 (d, 1H, J=8 Hz), 6.3 (d, 1H, J=8 Hz), 6.2 (s, 2H), 4.95 (s, 2H), and 3.8 (s, 3H). IR (KBr, cm^{-1}) 3364, 1739, 1630, 1582, 1500, 1455, 1285, 1232, 1153, and 774. MS (FD) m/e 438.

Elemental Analyses for $C_{27}H_{22}N_2O_4$:

Calculated: C, 73.97; H, 5.02; N, 6.39.
Found: C, 71.66; H, 5.14; N, 5.96.

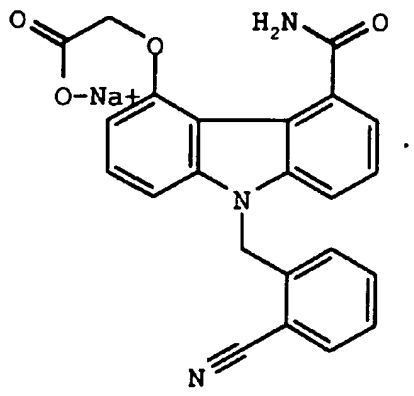
E. {9-[(1-Naphthyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, sodium salt.

A solution of the {9-[(1-naphthyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, methyl ester (21 mg, 0.048 mM) and 0.05 mL (0.05 mM) of 1 N NaOH in 5 mL of ethanol was stirred for 20 hours at 25 °C. The resultant white precipitate was collected by filtration, washed with a small amount of EtOH, then dried *in vacuo* to afford 17 mg (80%) of the {9-[(1-naphthyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, sodium salt as a white powder. ^{1}H NMR (DMSO-d6) δ 8.4 (d, 1H, J=8 Hz), 8.05 (d, 1H, J=8 Hz), 7.8 (d, 1H, J=8 Hz), 7.75-7.2 (m, 8H), 7.1 (d, 1H, J=8 Hz), 6.95 (d, 1H, J=8 Hz), 6.55 (d, 1H, J=8 Hz), 6.3 (d, 1H, J=8 Hz), 6.15 (s, 2H), and 4.4 (s, 2H). IR (KBr, cm^{-1}) 1664, 1615, 1595, 1455, 1408, 1324, 1275, and 775. MS (ES) m/e 423, 425.

Elemental Analyses for $C_{26}H_{19}N_2O_4Na$:
Calculated: C, 69.96; H, 4.26; N, 6.28.
Found: C, 67.91; H, 4.24; N, 5.76.

EXAMPLE 33

Preparation of {9-[(2-cyanophenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, sodium salt



A. 9-[(2-Cyanophenyl)methyl]-5-carbomethoxy-1,2-dihydrocarbazol-4(3H)-one

40% Methanolic Triton B (2.18 mL, 4.8 mM) was slowly added dropwise to a solution of 5-carbomethoxy-1,2-dihydro-9H-carbazol-4(3H)-one (973 mg, 4.0 mM) in 10 mL of DMF at 25 °C. After 10 minutes, a-bromo-*o*-tolunitrile (1.0 g, 5.0 mM) was added and the resultant mixture stirred at room temperature for 30 hours. The mixture was diluted with ethyl acetate, washed five times with H_2O, 1 N HCl, H_2O, sat $NaHCO_3$, H_2O, and saturated brine, dried over anhydrous magnesium sulfate, filtered, concentrated. The residue was triturated with diethyl ether and methylene chloride, then dried *in vacuo* to afford 1.31 g (91%) of the 9-[(2-cyanophenyl)methyl]-5-carbomethoxy-1,2-dihydrocarbazol-4(3H)-one as a tan solid. ^{1}H NMR ($CDCl_3$) δ 7.75 (dd, 1H, J=1 and 8 Hz), 7.5-7.2 (m, 5H), 6.6 (d, 1H, J=8 Hz), 5.55 (s, 2H), 4.05 (s, 3H), 2.85 (t, 2H, J=6 Hz), 2.6 (t, 2H, J=6 Hz), and 2.25 (m , 2H). IR (KBr, cm^{-1}) 2222, 1711, and 1650. MS (ES) m/e 357, 359.

Elemental Analyses for $C_{22}H_{18}N_2O_3$:

Calculated: C, 73.73; H, 5.06; N, 7.82.
Found: C, 73.62; H, 5.34; N, 7.59.

B. 9-[(2-Cyanophenyl)methyl]-4-hydroxy-5-carbomethoxy carbazole

A solution of the 9-[(2-cyanophenyl)methyl]-5-carbomethoxy-1,2-dihydrocarbazol-4(3H)-one (1.27 g, 3.5 mM) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (892 mg, 3.85 mM) in 25 mL of toluene was stirred at reflux for 7 hours. The mixture was purified directly by column chromatography on silica gel (elution with methylene chloride) to afford 305 mg (24%) of the 9-[(2-cyanophenyl)methyl]-4-hydroxy-5-carbomethyoxy carbazole as a yellow solid. ^{1}H NMR ($CDCl_3$) δ 10.35 (s, 1H), 8.0 (d, 1H, J=8 Hz), 7.75 (d, 1H, J=8 Hz), 7.5-7.2 (m, 5H), 6.85 (m, 2H), 6.6 (d, 1H, J=8 Hz), 5.75 (s, 2H), and 4.1 (s, 3H). IR ($CHCl_3$, cm^{-1}) 3025, 2223, and 1686. MS (ES) m/e 355, 357.

Elemental Analyses for $C_{22}H_{16}N_2O_3$:
Calculated: C, 74.15; H, 4.53; N, 7.86.
Found: C, 72.99; H, 4.41; N, 7.65.

C. 9-[(2-Cyanophenyl)methyl]-4-hydroxy-5-carbamoyl carbazole

A solution of the 9-[(2-cyanophenyl)methyl]-4-hydroxy-5-carbomethoxy carbazole (295 mg, 0.83 mM) in 5 mL THF and 20 mL concentrated aqueous ammonium hydroxide was sonicated for 22 hours at 40-50 °C. The mixture was diluted with ethyl acetate and acidified to pH 1 with 5 N HCl. The aqueous layer was extracted three times with ethyl acetate. The combined organic extracts were washed with H_2O and saturated brine, dried over magnesium sulfate, filtered, and concentrated. The residue was purified by column chromatography on silica gel (elution with gradient

hexanes/ethyl acetate) to afford 140 mg (49%) of the 9-[(2-cyanophenyl)methyl]-4-hydroxy-5-carbamoyl carbazole as a tan solid. ^{1}H NMR (DMSO-d6) δ 10.5 (s, 1H), 8.8 (br s, 1H), 8.4 (br s, 1H), 7.9 (d, 1H, J=8 Hz), 7.75 (d, 1H, J=8 Hz), 7.5-7.4 (m, 4H), 7.25 (t, 1H, J=8 Hz), 7.0 (d, 1H, J=8 Hz), 6.6 (d, 1H, J=8 Hz), 6.4 (m, 1H), and 5.85 (s, 2H). IR (KBr, cm^{-1}) 3448, 3356, 2225, 1628, and 1600. MS (ES) m/e 340, 342.

Elemental Analyses for $C_{21}H_{15}N_3O_2$:

Calculated: C, 73.89; H, 4.43; N, 12.31.

Found: C, 73.39; H, 4.56; N, 13.32.

D. {9-[(2-Cyanophenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, methyl ester

40% Methanolic Triton B (0.24 mL, 0.53 mM) was added to a solution of the 9-[(2-cyanophenyl)methyl]-4-hydroxy-5-carbamoyl carbazole (140 mg, 0.41 mM) in 5 mL DMF at room temperature. After 15 minutes, methyl bromoacetate (130 mg, 0.82 mM) was added and the resultant mixture stirred at room temperature for 24 hours. The mixture was diluted with ethyl acetate, washed four times with H_2O, 1 N HCl, H_2O, sat. $NaHCO_3$, and saturated brine, dried over magnesium sulfate, filtered, and concentrated. The residue was purified by column chromatography on silica gel (elution with gradient methylene chloride/ethyl acetate/THF) to afford 116 mg (68%) of the {9-[(2-cyanophenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, methyl ester as a white solid. ^{1}H NMR ($CDCl_3$) δ 7.75 (d, 1H, J=8 Hz), 7.5-7.2 (m, 6H), 6.95 (d, 1H, J=8 Hz), 6.6 (d, 2H, J=8 Hz),), 6.3 (br s, 1H), 6.1 (br s, 1H), 5.75 (s, 2H), 4.9 (s, 2H), and 3.8 (s, 3H). IR (KBr, cm^{-1}) 2228, 1732, and 1675. MS (ES) m/e 412, 414.

Elemental Analyses for $C_{24}H_{19}N_3O_4$:

Calculated: C, 69.72; H, 4.63; N, 10.16.

Found: C, 70.00; H, 4.69; N, 10.32.

E. {9-[(2-Cyanophenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, sodium salt

A suspension of the {9-[(2-cyanophenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, methyl ester (110 mg, 0.266 mM) and 0.29 mL (0.29 mM) of 1 N NaOH in 5 mL of ethanol was sonicated for 2 hours at 25 °C. The resultant white precipitate was collected by filtration, washed with small amounts of EtOH, diethyl ether, and hexanes, then dried *in vacuo* to afford 107 mg (95%) of the {9-[(2-cyanophenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, sodium salt as a white powder. ^{1}H NMR (DMSO-d6) δ 7.9 (d, 1H, J=8 Hz), 7.6 (br s, 1H), 7.5 (d, 1H, J=8 Hz), 7.45-7.4 (m, 3H), 7.35 (t, 1H, J=8 Hz), 7.25 (t, 1H, J=8 Hz), 7.1 (d, 1H, J=8 Hz), 7.05 (d, 1H, J=8 Hz), 6.55 (d, 1H, J=8 Hz), 6.4 (d, 1H, J=8 Hz), 5.8 (s, 2H), and 4.3 (s, 2H). IR (KBr, cm^{-1}) 2220, 1652, and 1613. MS (ES) m/e 398, 400.

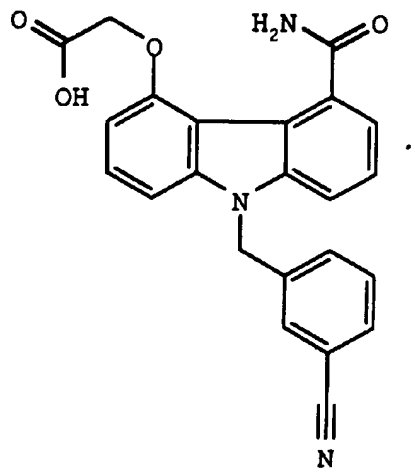
Elemental Analyses for $C_{23}H_{16}N_3O_4Na$:

Calculated: C, 65.56; H, 3.83; N, 9.97.

Found: C, 65.61; H, 3.71; N, 9.89.

EXAMPLE 34

Preparation of {9-[(3-cyanophenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid



A. 9-[(3-Cyanophenyl)methyl]-5-carbomethoxy-1,2-dihydrocarbazol-4(3H)-one

A suspension of 5-carbomethoxy-1,2-dihydro-9H-carbazol-4(3H)-one (973 mg, 4.0 mM), a-bromo-*m*-tolunitrile (1.0 g, 4.9 mM), and potassium carbonate (553 mg, 4.0 mM) in 10 mL of DMF was stirred at 25 °C for 24 hours. The mixture was diluted with ethyl acetate, washed five times with H_2O, 1 N HCl, H_2O, sat $NaHCO_3$, H_2O, and saturated brine, dried over anhydrous magnesium sulfate, filtered, concentrated. The residue was dried *in vacuo* to afford 1.18 g (82%) of the 9-[(3-cyanophenyl)methyl]-5-carbomethoxy -1,2-dihydrocarbazol-4(3H)-one as a tan solid. ^1H NMR ($CDCl_3$) δ 7.65-7.2 (m, 6H), 7.15 (d, 1H, J=8 Hz), 5.4 (s, 2H), 4.05 (s, 3H), 2.85 (t, 2H, J=6 Hz), 2.6 (t, 2H, J=6 Hz), and 2.25 (m, 2H). IR (KBr, cm^{-1}) 2226, 1729, and 1646. MS (ES) m/e 357, 359.

Elemental Analyses for $C_{22}H_{18}N_2O_3$:

Calculated:	C, 73.73; H, 5.06; N, 7.82.
Found:	C, 70.18; H, 4.97; N, 7.07.

B. 9-[(3-Cyanophenyl)methyl]-4-hydroxy-5-carbomethoxy carbazole

A solution of the 9-[(3-cyanophenyl)methyl]-5-carbomethoxy-1,2-dihydrocarbazol-4(3H)-one (1.15 g, 3.2 mM) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (815 mg, 3.52 mM) in 25 mL of toluene was stirred at reflux for 2 hours. The mixture was purified directly by column chromatography on silica gel (elution with methylene chloride) to afford 120 mg (10%) of the 9-[(3-cyanophenyl)methyl]-4-hydroxy-5-carbomethyoxy carbazole as a yellow solid. ^{1}H NMR ($CDCl_3$) δ 10.35 (s, 1H), 8.0 (d, 1H, J=8 Hz), 7.6-7.2 (m, 7H), 6.85 (m, 2H), 5.55 (s, 2H), and 4.1 (s, 3H). IR (KBr, cm^{-1}) 3063, 3025, 2234, and 1685. MS (ES) m/e 355, 357.

Elemental Analyses for $C_{22}H_{16}N_2O_3$:

Calculated: C, 74.15; H, 4.53; N, 7.86.

Found: C, 73.36; H, 4.51; N, 8.06.

C. 9-[(3-Cyanophenyl)methyl]-4-hydroxy-5-carbamoyl carbazole

A solution of the 9-[(3-cyanophenyl)methyl]-4-hydroxy-5-carbomethoxy carbazole (114 mg, 0.32 mM) in 5 mL THF and 20 mL concentrated aqueous ammonium hydroxide was sonicated for 7 hours at 40-50 °C. The mixture was diluted with ethyl acetate and acidified to pH 1 with 5 N HCl. The aqueous layer was extracted three times with ethyl acetate. The combined organic extracts were washed with H_2O and saturated brine, dried over magnesium sulfate, filtered, and concentrated. The residue was purified by column chromatography on silica gel (elution with gradient hexanes/ethyl acetate) to afford 40 mg (49%) of the 9-[(3-cyanophenyl)methyl]-4-hydroxy-5-carbamoyl carbazole as a

white solid. ^{1}H NMR (DMSO-d6) δ 10.5 (s, 1H), 8.8 (br s, 1H), 8.4 (br s, 1H), 7.8 (d, 1H, J=8 Hz), 7.7 (d, 1H, J=8 Hz), 7.6 (s, 1H), 7.5-7.4 (m, 3H), 7.3 (t, 1H, J=8 Hz), 7.25 (d, 1H, J=8 Hz), 7.1 (d, 1H, J=8 Hz), 6.6 (d, 1H, J=8 Hz), and 5.75 (s, 2H). IR (KBr, cm^{-1}) 3430, 3347, 2231, 1628, and 1601. MS (ES) m/e 340, 342.

Elemental Analyses for $C_{21}H_{15}N_3O_2$:

Calculated: C, 73.89; H, 4.43; N, 12.31.

Found: C, 75.20; H, 4.80; N, 12.15.

D. {9-[(3-Cyanophenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, tert-butyl ester

40% Methanolic Triton B (0.06 mL, 0.13 mM) was added to a solution of the 9-[(3-cyanophenyl)methyl]-4-hydroxy-5-carbamoyl carbazole (34.1 mg, 0.1 mM) in 5 mL DMF at room temperature. After 1 minute, tert-butyl bromoacetate (40 mg, 0.2 mM) was added and the resultant mixture stirred at room temperature for 24 h. The mixture was diluted with ethyl acetate, washed four times with H_2O, 1 N HCl, H_2O, sat. $NaHCO_3$, and saturated brine, dried over magnesium sulfate, filtered, and concentrated. The residue was triturated with hexane to afford 51 mg (100%) of the {9-[(3-cyanophenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, tert-butyl ester as a white solid. ^{1}H NMR ($CDCl_3$) δ 7.55 (d, 1H, J=8 Hz), 7.5-7.2 (m, 7H), 6.95 (d, 1H, J=8 Hz), 6.6 (d, 1H, J=8 Hz), 6.3 (br s, 1H), 6.1 (br s, 1H), 5.5 (s, 2H), 4.8 (s, 2H), and 1.5 (s, 9H). IR (KBr, cm^{-1}) 2228, 1748, and 1669. MS (ES) m/e 455, 456.

Elemental Analyses for $C_{27}H_{25}N_3O_4$:

Calculated: C, 71.19; H, 5.53; N, 9.22.

Found: C, 70.24; H, 5.68; N, 8.96.

E. {9-[(3-Cyanophenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid

A solution of the {9-[(3-cyanophenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, tert-butyl ester (45 mg, 0.1 mM)) in 3 mL of trifluoroacetic acid was stirred at room temperature for 2 hours. The solvent was removed *in vacuo*. The residue was triturated with ethyl ether-hexanes, then dried *in vacuo* to afford 41 mg (100%) of the {9-[(2-cyanophenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid as a tan powder. ^{1}H NMR (DMSO-d6) δ 13.0 (br s, 1H), 7.6-7.3 (m, 10H), 7.1 (d, 1H, J=8 Hz), 6.65 (d, 1H, J=8 Hz), 5.8 (s, 2H), and 4.8 (s, 2H). IR (KBr, cm^{-1}) 2226, 1733, and 1640. MS (ES) m/e 398, 400.

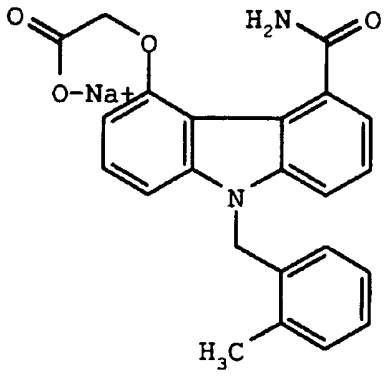
Elemental Analyses for $C_{23}H_{17}N_3O_4$:

Calculated: C, 69.17; H, 4.29; N, 10.52.

Found: C, 66.96; H, 4.37; N, 10.03.

EXAMPLE 35

Preparation of {9-[(2-methylphenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, sodium salt



A. 9-[(2-Methylphenyl)methyl]-5-carbomethoxy-1,2-dihydrocarbazol-4(3H)-one

A suspension of 5-carbomethoxy-1,2-dihydro-9H-carbazol-4(3H)-one (870 mg, 3.58 mM), a-bromo-*o*-xylene (662 mg, 3.58 mM), and potassium carbonate (500 mg, 3.61 mM) in 20 mL DMF was stirred at room temperature for 20 hours. The mixture was diluted with ethyl acetate, washed with H_2O and saturated brine, dried over anhydrous magnesium sulfate, filtered, concentrated to afford 1.21 g (98%) of the 9-[(2-methylphenyl)methyl]-5-carbomethoxy-1,2-dihydrocarbazol-4(3H)-one as a dark oil. ^{1}H NMR (DMSO-d6) δ 7.5-7.2 (m, 4H), 7.15 (t, 1H, J=8 Hz), 7.0 (t, 1H, J=8 Hz), 6.15 (d, 1H, J=8 Hz), 5.55 (s, 2H), 3.85 (s, 3H), 2.6 (m, 2H), 2.4 (m, 2H), 2.4 (s, 3H), and 2.1 (m, 2H). IR ($CHCl_3$, cm^{-1}) 3010, 2952, 1724, 1671, 1653, 1604, 1460, 1444, 1290, 1174, and 1122. MS (ES) m/e 348.5.

Elemental Analyses for $C_{22}H_{21}NO_3$:

Calculated:	C, 76.08; H, 6.05; N, 4.03.
Found	C, 73.33; H, 6.36; N, 4.30.

B. 9-[(2-Methylphenyl)methyl]-4-hydroxy-5-carbomethoxy carbazole

A solution of the 9-[(2-methylphenyl)methyl]-5-carbomethoxy-1,2-dihydrocarbazol-4(3H)-one (1.2 g, 3.5 mM) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (800 mg, 3.6 mM) in 70 mL of toluene was stirred at 80-90 °C for 5 hours. The mixture was purified directly by column chromatography on silica gel (elution with methylene chloride) to afford 260 mg (22%) of the 9-[(2-methylphenyl)methyl]-4-hydroxy-5-carbomethyoxy carbazole as a yellow solid. ^{1}H NMR (DMSO-d6) δ 10.25 (s, 1H), 7.5 (d, 1H, J=8 Hz), 7.4 (t, 1H, J=8 Hz), 7.3-7.1 (m, 4H), 6.9 (m, 2H), 6.6 (d, 1H, J=8 Hz), 6.1 (d, 1H, J=8 Hz), 5.65 (s, 2H), 3.8 (s, 3H), and 2.5 (s, 3H). IR (KBr, cm^{-1}) 3200, 1672, 1440, 1426, 1332, 1302, 1265, 1216, 1141, 761, 749, and 718. MS (ES) m/e 344, 346.

Elemental Analyses for $C_{22}H_{19}NO_3$:

Calculated: C, 76.52; H, 5.51; N, 4.06.

Found: C, 76.44; H, 5.66; N, 3.94.

C. 9-[(2-Methylphenyl)methyl]-4-hydroxy-5-carbamoyl carbazole

A solution of the 9-[(2-methylphenyl)methyl]-4-hydroxy-5-carbomethoxy carbazole (260 mg, 0.75 mM) in 10 mL THF and 30 mL concentrated aqueous ammonium hydroxide was sonicated for 5 hours at 40-50 °C. The mixture was diluted with ethyl acetate and acidified to pH 1 with 5 N HCl. The aqueous layer was extracted three times with ethyl acetate. The combined organic extracts were washed with H_2O and saturated brine, dried over magnesium sulfate, filtered, and concentrated. The residue was purified by column chromatography on silica gel (elution with gradient hexanes/ethyl acetate) to afford 90 mg (36%) of the 9-[(2-methylphenyl)methyl]-4-hydroxy-5-carbamoyl carbazole as a tan solid. ^{1}H NMR (DMSO-d6) δ 10.5 (s, 1H), 8.8 (br s, 1H), 8.4 (br s, 1H), 7.7 (m, 1H), 7.5 (m, 2H), 7.3 (m, 2H), 7.1 (t, 1H, J=8 Hz), 6.95 (d, 1H, J=8 Hz), 6.85 (t, 1H, J=8 Hz), 6.6 (d, 1H, J=8 Hz), 5.95 (d, 1H, J=8 Hz), 5.7 (s, 2H), and 2.5 (s, 3H). IR (KBr, cm^{-1}) 3451, 3191, 1627, 1600, 1584, 1562, 1435, 1329, 1322, 1263, and 774. MS (ES) m/e 329, 331.

Elemental Analyses for $C_{21}H_{18}N_2O_2$:

Calculated: C, 76.36; H, 5.45; N, 8.48.

Found: C, 75.66; H, 5.79; N, 8.07.

D. {9-[(2-Methylphenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, methyl ester

40% Methanolic Triton B (0.45 mL, 0.99 mM) was added to a solution of the 9-[(2-methylphenyl)methyl]-4-hydroxy-5-

carbamoyl carbazole (80 mg, 0.24 mM) in 8 mL DMF at room temperature. After 3 minutes, methyl bromoacetate (115 mg, 0.72 mM) was added and the resultant mixture stirred at room temperature for 48 hours. The mixture was diluted with ethyl acetate, washed with H_2O, 1 N HCl, H_2O, and saturated brine, dried over magnesium sulfate, filtered, and concentrated. The residue was purified by column chromatography on silica gel (elution with ethyl acetate) to afford 80 mg (82%) of the {9-[(2-methylphenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, methyl ester as a white solid. ^{1}H NMR (DMSO-d6) δ 7.56 (br s, 1H), 7.5-7.1 (m, 9H), 6.9 (t, 1H, J=8 Hz), 6.6 (d, 1H, J=8 Hz), 5.65 (s, 2H), 4.9 (s, 2H), 3.8 (s, 3H), and 2.5 (s, 3H). IR (KBr, cm^{-1}) 3367, 3153, 1760, 1740, 1672, 1644, 1619, 1591, 1578, 1498, 1456, 1425, 1327, 1200, 1153, 1109, 1100, and 777. MS (FD) m/e 402.

Elemental Analyses for $C_{24}H_{22}N_2O_4$:

Calculated:	C, 71.64; H, 5.47; N, 6.96.
Found:	C, 71.51; H, 5.56; N, 6.67.

E. {9-[(2-Methylphenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, sodium salt

A suspension of the {9-[(2-methylphenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, methyl ester (15.5 mg, 0.039 mM) and 0.04 mL (0.04 mM) of 1 N NaOH in 5 mL of ethanol was stirred for 24 hours at 25 °C. The resultant white precipitate was collected by filtration, washed with a small amount of EtOH, then dried *in vacuo* to afford 10 mg (63%) of the {9-[(2-methylphenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, sodium salt as a white powder. ^{1}H NMR (DMSO-d6) δ 7.55 (br s, 1H), 7.5-7.0 (m, 7H), 6.9 (d, 1H, J=8 Hz), 6.85 (t, 1H, J=8 Hz), 6.6 (d, 1H, J=8 Hz), 6.2 (d, 1H, J=8 Hz), 5.6 (s, 2H), 4.35 (s, 2H),

and 2.5 (s, 3H). IR (KBr, cm^{-1}) 3390, 1656, 1613, 1595, 1573, 1498, 1455, 1408, 1325, 1332, and 719. MS (ES) m/e 387, 389.

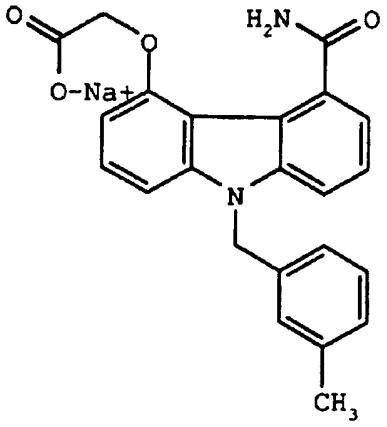
Elemental Analyses for $C_{23}H_{19}N_2O_4$:

Calculated: C, 67.32; H, 4.63; N, 6.83.

Found: C, 64.72; H, 4.44; N, 6.40.

EXAMPLE 36

Preparation of {9-[(3-methylphenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, sodium salt



A. 9-[(3-Methylphenyl)methyl]-5-carbomethoxy-1,2-dihydrocarbazol-4(3H)-one

A suspension of 5-carbomethoxy-1,2-dihydro-9H-carbazol-4(3H)-one (870 mg, 3.58 mM), a-bromo-*m*-xylene (662 mg, 3.58 mM), and potassium carbonate (500 mg, 3.61 mM) in 20 mL DMF was stirred at room temperature for 16 hours. The mixture was diluted with ethyl acetate, washed with H_2O and saturated brine, dried over anhydrous magnesium sulfate, filtered, concentrated to afford 1.18 g (95%) of the 9-[(3-methylphenyl)methyl]-5-carbomethoxy-1,2-dihydrocarbazol-4(3H)-one as a dark oil. ^1H NMR (DMSO-d6) δ 7.65 (dd, 1H, J=1 and 8 Hz), 7.3-7.1 (m, 3H), 7.05 (d, 1H, J=8 Hz), 7.0

(s, 1H), 6.85 (d, 1H, J=8 Hz), 5.5 (s, 2H), 3.8 (s, 3H), 3.0 (m, 2H), 2.45 (m, 2H), 2.3 (s, 3H), and 2.1 (m, 2H). IR ($CHCl_3$, cm^{-1}) 3010, 2953, 1724, 1652, 1605, 1465, 1442, 1288, 1174, and 1119. MS (ES) m/e 348.5.

Elemental Analyses for $C_{22}H_{21}NO_3$:

Calculated: C, 76.08; H, 6.05; N, 4.03.
Found: C, 74.53; H, 6.03; N, 3.68.

B. 9-[(3-Methylphenyl)methyl]-4-hydroxy-5-carbomethoxy carbazole

A solution of the 9-[(3-methylphenyl)methyl]-5-carbomethoxy-1,2-dihydrocarbazol-4(3H)-one (1.18 g, 3.4 mM) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (800 mg, 3.6 mM) in 70 mL of toluene was stirred at 80-90 °C for 6 hours. The mixture was purified directly by column chromatography on silica gel (elution with methylene chloride) to afford 300 mg (26%) of the 9-[(3-methylphenyl)methyl]-4-hydroxy-5-carbomethyoxy carbazole as a yellow solid. ^1H NMR (DMSO-d6) δ 10.2 (s, 1H), 7.65 (d, 1H, J=8 Hz), 7.35 (t, 1H, J=8 Hz), 7.25 (t, 1H, J=8 Hz), 7.2-7.0 (m, 4H), 6.9 (m, 2H), 6.6 (d, 1H, J=8 Hz), 5.6 (s, 2H), 3.85 (s, 3H), and 2.2 (s, 3H). IR (KBr, cm^{-1}) 3200, 1673, 1596, 1440, 1426, 1394, 1265, 1216, 1152, 750, 711, and 694. MS (ES) m/e 344, 346.

Elemental Analyses for $C_{22}H_{19}NO_3$:

Calculated: C, 76.52; H, 5.51; N, 4.06.
Found: C, 76.22; H, 5.55; N, 3.97.

C. 9-[(3-Methylphenyl)methyl]-4-hydroxy-5-carbamoyl carbazole

A solution of the 9-[(3-methylphenyl)methyl]-4-hydroxy-5-carbomethoxy carbazole (300 mg, 0.87 mM) in 10 mL THF and 30 mL concentrated aqueous ammonium hydroxide was sonicated

for 5 hours at 40-50 °C. The mixture was diluted with ethyl acetate and acidified to pH 1 with 5 N HCl. The aqueous layer was extracted three times with ethyl acetate. The combined organic extracts were washed with H_2O and saturated brine, dried over magnesium sulfate, filtered, and concentrated. The residue was purified by column chromatography on silica gel (elution with gradient hexanes/ethyl acetate) to afford 114 mg (40%) of the 9-[(3-methylphenyl)methyl]-4-hydroxy-5-carbamoyl carbazole as an off-white solid. ^{1}H NMR (DMSO-d6) δ 10.5 (s, 1H), 8.8 (br s, 1H), 8.4 (br s, 1H), 7.8 (dd, 1H, J=1 and 8 Hz), 7.4 (m, 2H), 7.3 (t, 1H, J=8 Hz), 7.15-7.0 (m, 3H), 6.85 (d, 1H, J=8 Hz), 6.6 (d, 1H, J=8 Hz), 5.95 (d, 1H, J=8 Hz), 5.65 (s, 2H), and 2.25 (s, 3H). IR (KBr, cm^{-1}) 3434, 3203, 1629, 1599, 1579, 1552, 1443, 1330, 1262, 1214, and 776. MS (ES) m/e 329, 331.

Elemental Analyses for $C_{21}H_{18}N_2O_2$:

Calculated: C, 76.36; H, 5.45; N, 8.48.

Found: C, 77.56; H, 5.67; N, 8.26.

D. {9-[(3-Methylphenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, methyl ester

40% Methanolic Triton B (0.45 mL, 0.99 mM) was added to a solution of the 9-[(3-methylphenyl)methyl]-4-hydroxy-5-carbamoyl carbazole (100 mg, 0.30 mM) in 8 mL DMF at room temperature. After 3 minutes, methyl bromoacetate (115 mg, 0.72 mM) was added and the resultant mixture stirred at room temperature for 24 hours. The mixture was diluted with ethyl acetate, washed with H_2O, and saturated brine, dried over magnesium sulfate, filtered, and concentrated. The residue was purified by column chromatography on silica gel (elution with ethyl acetate) to afford 80 mg (66%) of the {9-[(3-methylphenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic

acid, methyl ester as a white solid. ^{1}H NMR (DMSO-d6) δ 7.6 (d, 1H, J=8 Hz), 7.55 (br s, 1H), 7.45-7.0 (m, 8H), 6.9 (d, 1H, J=8 Hz), 6.6 (d, 1H, J=8 Hz), 5.65 (s, 2H), 4.9 (s, 2H), 3.75 (s, 3H), and 2.2 (s, 3H). IR (KBr, cm^{-1}) 3367, 3157, 1760, 1642, 1589, 1499, 1455, 1424, 1328, 1216, 1151, 1102, 772, and 714. MS (FD) m/e 402.

Elemental Analyses for $C_{24}H_{22}N_2O_4$:

Calculated: C, 71.64; H, 5.47; N, 6.96.

Found: C, 71.01; H, 5.60; N, 6.66.

E. {9-[(3-Methylphenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, sodium salt

A suspension of the {9-[(3-methylphenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, methyl ester (15.8 mg, 0.039 mM) and 0.04 mL (0.04 mM) of 1 N NaOH in 5 mL of ethanol was stirred for 24 h at 25 °C. The resultant white precipitate was collected by filtration, washed with a small amount of EtOH, then dried *in vacuo* to afford 10 mg (62%) of the {9-[(3-methylphenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, sodium salt as a white powder. ^{1}H NMR (DMSO-d6) δ 7.55 (d, 1H, J=8 Hz), 7.5-7.0 (m, 9H), 6.85 (d, 1H, J=8 Hz), 6.55 (d, 1H, J=8 Hz), 5.6 (s, 2H), 4.35 (s, 2H), and 2.2 (s, 3H). IR (KBr, cm^{-1}) 3390, 1656, 1613, 1595, 1573, 1498, 1455, 1408, 1325, 1332, and 719. MS (ES) m/e 387, 389.

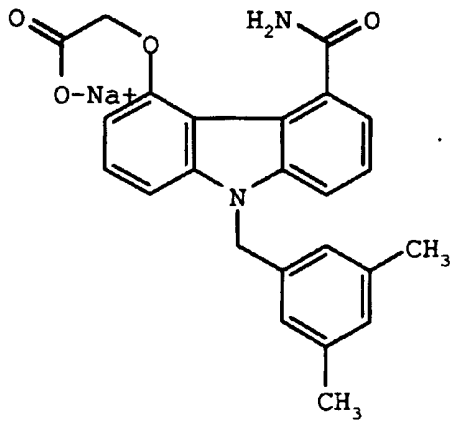
Elemental Analyses for $C_{23}H_{19}N_2O_4Na$:

Calculated: C, 67.32; H, 4.63; N, 6.83.

Found: C, 61.20; H, 4.64; N, 6.06.

EXAMPLE 37

Preparation of {9-[(3,5-dimethylphenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, sodium salt



A. 9-[(3,5-Dimethylphenyl)methyl]-5-carbomethoxy-1,2-dihydrocarbazol-4(3H)-one

A suspension of 5-carbomethoxy-1,2-dihydro-9H-carbazol-4(3H)-one (850 mg, 3.5 mM), 3,5-dimethylbenzyl bromide (765 mg, 3.8 mM), and potassium carbonate (500 mg, 3.61 mM) in 25 mL DMF was stirred at room temperature for 19 hours. The mixture was diluted with ethyl acetate, washed with H_2O and saturated brine, dried over anhydrous magnesium sulfate, filtered, concentrated. The residue was purified by column chromatography on silica gel (elution with ethyl acetate) to afford 0.84 g (67%) of the 9-[(3,5-dimethylphenyl)methyl]-5-carbomethoxy-1,2-dihydrocarbazol-4(3H)-one as a foam. ^1H NMR (DMSO-d6) δ 7.7 (dd, 1H, J=1 and 8 Hz), 7.3-7.2 (m, 2H), 6.9 (s, 1H), 6.75 (s, 2H), 5.45 (s, 2H), 3.8 (s, 3H), 3.0 (m, 2H), 2.45 (m, 2H), 2.2 (s, 6H), and 2.1 (m, 2H). IR (KBr, cm^{-1}) 1726, 1653, 1602, 1465, 1442, 1282, 1172, and 1116. MS (ES) m/e 362.

Elemental Analyses for $C_{23}H_{23}NO_3$:

Calculated:	C, 76.45; H, 6.37; N, 3.88.
Found:	C, 76.82; H, 6.54; N, 3.91.

B. 9-[(3,5-Dimethylphenyl)methyl]-4-hydroxy-5-carbomethoxy carbazole

A solution of the 9-[(3,5-dimethylphenyl)methyl]-5-carbomethoxy-1,2-dihydrocarbazol-4(3H)-one (0.8 g, 2.2 mM) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (550 mg, 2.43 mM) in 70 mL of toluene was stirred at 80-90 °C for 5 hours. The mixture was purified directly by column chromatography on silica gel (elution with methylene chloride) to afford 234 mg (29%) of the 9-[(3,5-dimethylphenyl)methyl]-4-hydroxy-5-carbomethyoxy carbazole as a yellow solid. ^{1}H NMR (DMSO-d6) δ 10.2 (s, 1H), 7.65 (d, 1H, J=8 Hz), 7.35 (t, 1H, J=8 Hz), 7.25 (t, 1H, J=8 Hz), 7.15 (d, 1H, J=8 Hz), 7.05 (d, 1H, J=8 Hz), 6.9 (s, 1H), 6.7 (s, 2H), 6.6 (d, 1H, J=8 Hz), 5.6 (s, 2H), 3.85 (s, 3H), and 2.2 (s, 6H). IR (KBr, cm^{-1}) 3016, 1675, 1598, 1441, 1426, 1394, 1288, 1270, 1221, 1152, 754, and 713. MS (ES) m/e 358, 360.

Elemental Analyses for $C_{23}H_{21}NO_3$:

Calculated: C, 76.88; H, 5.85; N, 3.90.

Found: C, 76.94; H, 6.00; N, 3.93.

C. 9-[(3,5-Dimethylphenyl)methyl]-4-hydroxy-5-carbamoyl carbazole

A solution of the 9-[(3,5-dimethylphenyl)methyl]-4-hydroxy-5-carbomethoxy carbazole (200 mg, 0.55 mM) in 10 mL THF and 30 mL concentrated aqueous ammonium hydroxide was sonicated for 4 days at 40-50 °C. The mixture was diluted with ethyl acetate and acidified to pH 2.5 with 5 N HCl. The aqueous layer was extracted three times with ethyl acetate. The combined organic extracts were washed with saturated brine, dried over magnesium sulfate, filtered, and concentrated. The residue was purified by column chromatography on silica gel (elution with gradient hexanes/ethyl acetate) to afford 90 mg (47%) of the 9-[(3,5-

dimethylphenyl)methyl]-4-hydroxy-5-carbamoyl carbazole as an off-white solid. ^{1}H NMR (DMSO-d6) δ 10.5 (s, 1H), 8.6 (s, 1H), 8.4 (s, 1H), 7.75 (d, 1H, J=8 Hz), 7.45 (m, 2H), 7.3 (t, 1H, J=8 Hz), 7.1 (d, 1H, J=8 Hz), 6.85 (s, 1H), 6.7 (s, 2H), 6.6 (d, 1H, J=8 Hz), 5.6 (s, 2H), and 2.2 (s, 6H). IR (KBr, cm^{-1}) 3417, 3198, 3113, 3063, 1631, 1601, 1562, 1438, 1332, 1263, 1217, 781, and 773. MS (ES) m/e 343, 345.

Elemental Analyses for $C_{22}H_{20}N_2O_2$:

Calculated: C, 76.74; H, 5.81; N, 8.14.

Found: C, 76.97; H, 5.94; N, 7.95.

D. {9-[(3,5-Dimethylphenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, methyl ester

40% Methanolic Triton B (0.13 mL, 0.28 mM) was added to a solution of the 9-[(3,5-dimethylphenyl)methyl]-4-hydroxy-5-carbamoyl carbazole (80 mg, 0.23 mM) in 8 mL DMF at room temperature. After 3 minutes, methyl bromoacetate (43 mg, 0.28 mM) was added and the resultant mixture stirred at room temperature for 17 hours. The mixture was diluted with ethyl acetate, washed with H_2O, and saturated brine, dried over magnesium sulfate, filtered, and concentrated. The residue was purified by column chromatography on silica gel (elution with ethyl acetate) to afford 70 mg (72%) of the {9-[(3,5-dimethylphenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, methyl ester as a white solid. ^{1}H NMR (DMSO-d6) δ 7.6 (d, 1H, J=8 Hz), 7.55 (br s, 1H), 7.45-7.3 (m, 2H), 7.25 (d, 1H, J=8 Hz), 7.2 (br s, 1H), 7.1 (d, 1H, J=8 Hz), 6.9 (s, 1H), 6.8 (s, 2H), 6.6 (d, 1H, J=8 Hz), 5.65 (s, 2H), 4.9 (s, 2H), 3.75 (s, 3H), and 2.2 (s, 6H). IR (KBr, cm^{-1}) 3362, 3173, 1758, 1638, 1583, 1500, 1454, 1434, 1330, 1215, 1151, 1106, 772, 715, and 706. MS (FD) m/e 417.

Elemental Analyses for $C_{25}H_{24}N_2O_4$:

Calculated: C, 72.12; H, 5.76; N, 6.73.

Found: C, 71.80; H, 5.60; N, 6.73.

E. {9-[(3,5-Dimethylphenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, sodium salt

A suspension of the {9-[(3,5-dimethylphenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, methyl ester (18 mg, 0.043 mM) and 0.043 mL (0.043 mM) of 1 N NaOH in 5 mL of ethanol was stirred for 42 hours at 25 °C. The resultant white precipitate was collected by filtration, washed with a small amount of EtOH, then dried *in vacuo* to afford 12 mg (67%) of the {9-[(3,5-dimethylphenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, sodium salt as a white powder. ^{1}H NMR (DMSO-d6) δ 7.6 (d, 1H, J=8 Hz), 7.5-7.3 (m, 4H), 7.1 (m, 2H), 6.9 (s, 1H), 6.8 (s, 2H), 6.6 (d, 1H, J=8 Hz), 5.65 (s, 2H), 4.35 (s, 2H), and 2.2 (s, 6H). IR (KBr, cm^{-1}) 3385, 1663, 1616, 1575, 1498, 1456, 1412, and 1330. MS (ES) m/e 401, 403.

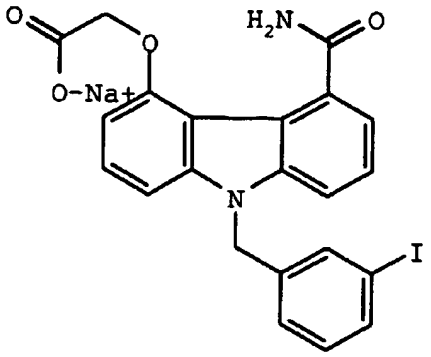
Elemental Analyses for $C_{24}H_{21}N_2O_4Na$:

Calculated: C, 67.92; H, 4.95; N, 6.60.

Found: C, 66.53; H, 5.06; N, 6.37.

EXAMPLE 38

Preparation of {9-[(3-iodophenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, sodium salt



A. 9-[(3-Iodophenyl)methyl]-5-carbomethoxy-1,2-dihydrocarbazol-4(3H)-one

A suspension of 5-carbomethoxy-1,2-dihydro-9H-carbazol-4(3H)-one (680 mg, 3.5 mM), 3-iodobenzyl bromide (1.2 g, 4.7 mM), and potassium carbonate (500 mg, 3.61 mM) in 20 mL DMF was stirred at room temperature for 18 hours. The mixture was diluted with ethyl acetate, washed with H_2O and saturated brine, dried over anhydrous magnesium sulfate, filtered, concentrated. The residue was purified trituration with methylene chloride-diethyl ether) to afford 0.70 g (55%) of the 9-[(3-iodophenyl)methyl]-5-carbomethoxy-1,2-dihydrocarbazol-4(3H)-one as a white solid. ^{1}H NMR (DMSO-d6) δ 7.7-7.6 (m, 3H), 7.2 (m, 2H), 7.1 (t, 1H, J=8 Hz), 6.95 (d, 1H, J=8Hz), 5.6 (s, 2H), 3.8 (s, 3H), 3.0 (t, 2H, J=6 Hz), 2.5 (t, 2H, J=6 Hz), and 2.2 (m , 2H). IR (KBr, cm^{-1}) 1732, 1639, 1441, 1421, 1273, 1117, and 763. MS (ES) m/e 458, 460.

Elemental Analyses for $C_{21}H_{18}NO_3I$:

Calculated: C, 54.90; H, 3.92; N, 3.05.

Found: C, 54.92; H, 3.98; N, 2.97.

B. 9-[(3-Iodophenyl)methyl]-4-hydroxy-5-carbomethoxy carbazole

A solution of the 9-[(3-iodophenyl)methyl]-5-carbomethoxy-1,2-dihydrocarbazol-4(3H)-one (700 mg, 1.52 mM) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (380 mg, 1.67 mM) in 70 mL of toluene was stirred between 70-80 °C for 5 hours. The mixture was purified directly by column chromatography on silica gel (elution with methylene chloride) to afford 220 mg (31%) of the 9-[(3-iodophenyl)methyl]-4-hydroxy-5-carbomethyoxy carbazole as a yellow foam. ^{1}H NMR (DMSO-d6) δ 10.25 (s, 1H), 7.7 (d, 1H, J=8 Hz), 7.6 (m, 2H), 7.4 (t, 1H, J=8 Hz), 7.25 (t, 1H,

J=8 Hz), 7.2 (d, 1H, J=8 Hz), 7.1 (m, 3H), 6.65 (d, 1H, J=8 Hz), 5.65 (s, 2H), and 3.8 (s, 3H). IR (KBr, cm^{-1}) 3377 (br), 3028, 1711, 1672, 1621, 1580, 1565, 1495, 1459, 1439, 1423, 1332, 1287, 1267, 1135, 773, 752, 712, and 688. MS (ES) m/e 456, 458.

Elemental Analyses for $C_{21}H_{16}NO_3I$:

Calculated: C, 55.14; H, 3.50; N, 3.06.

Found: C, 56.18; H, 3.87; N, 3.32.

C. 9-[(3-Iodophenyl)methyl]-4-hydroxy-5-carbamoyl carbazole

A solution of the 9-[(3-iodophenyl)methyl]-4-hydroxy-5-carbomethoxy carbazole (170 mg, 0.37 mM) in 10 mL THF and 30 mL concentrated aqueous ammonium hydroxide was stirred vigorously at room temperature for 120 hours. The mixture was diluted with ethyl acetate and acidified to pH 2 with 5 N HCl. The aqueous layer was extracted twice with ethyl acetate. The combined organic extracts were washed with saturated brine, dried over magnesium sulfate, filtered, and concentrated. The residue was purified by column chromatography on silica gel (elution with gradient methylene chloride/ethyl acetate) to afford 61 mg (37%) of the 9-[(3-iodophenyl)methyl]-4-hydroxy-5-carbamoyl carbazole as a white solid. ^1H NMR (DMSO-d6) δ 10.5 (s, 1H), 8.8 (br s, 1H), 8.4 (br s, 1H), 7.8 (dd, 1H, J=1 and 8 Hz), 7.6-7.4 (m, 4H), 7.3 (t, 1H, J=8 Hz), 7.1-6.9 (m, 3H), 6.6 (d, 1H, J=8 Hz), and 5.7 (s, 2H). IR ($CHCl_3$, cm^{-1}) 3423, 3201 (br), 1630, 1600, 1579, 1564, 1445, 1330, 1261, and 775. MS (ES) m/e 441, 443.

Elemental Analyses for $C_{20}H_{15}N_2O_2I$:

Calculated: C, 54.30; H, 3.39; N, 6.33.

Found: C, 54.92; H, 3.81; N, 6.08.

D. {9-[(3-Iodophenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, methyl ester

40% Methanolic Triton B (0.07 mL, 0.15 mM) was added to a solution of the 9-[(3-iodophenyl)methyl]-4-hydroxy-5-carbamoyl carbazole (60 mg, 0.13 mM) in 8 mL DMF at room temperature. After 3 minutes, methyl bromoacetate (30 mg, 0.19 mM) was added and the resultant mixture stirred at room temperature for 17 hours. The mixture was diluted with ethyl acetate, washed with H_2O and saturated brine, dried over magnesium sulfate, filtered, and concentrated. The residue was purified by column chromatography on silica gel (elution with ethyl acetate) to afford 60 mg (86%) of the {9-[(3-iodophenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, methyl ester as a white solid. ^{1}H NMR (DMSO-d6) δ 7.6-7.0 (m, 11H), 6.6 (d, 1H, J=8 Hz), 5.7 (s, 2H), 4.9 (s, 2H), and 3.75 (s, 3H). IR (KBr, cm^{-1}) 3500, 3350, 1727, 1642, 1291, 1236, and 772. MS (ES) m/e 515.

Elemental Analyses for $C_{23}H_{19}N_2O_4I$:

Calculated: C, 53.70; H, 3.70; N, 5.45.

Found: C, 53.92; H, 3.72; N, 5.32.

E. {9-[(3-Iodophenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid

A suspension of the {9-[(3-iodophenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, methyl ester (15 mg, 0.03 mM) and 0.03 mL (0.03 mM) of 1 N NaOH in 5 mL of ethanol was stirred for 43 hours at 25 °C, then cooled in an ice-bath. The resultant white precipitate was collected by filtration, washed with a small amount of EtOH, then dried *in vacuo* to afford 6.5 mg (43%) of the {9-[(3-iodophenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, sodium salt as a white powder. ^{1}H NMR (DMSO-d6) δ 7.6-7.0 (m, 11H), 6.6 (d, 1H, J=8 Hz), 5.7 (s, 2H), and 4.35 (s,

2H). IR (KBr, cm^{-1}) 3456, 3416, 3335, 1735, 1638, 1617, 1580, 1499, 1452, 1431, 1431, 1329, 1255, 1157, 772, 764, and 717. MS (ES) m/e 407, 409, 411.

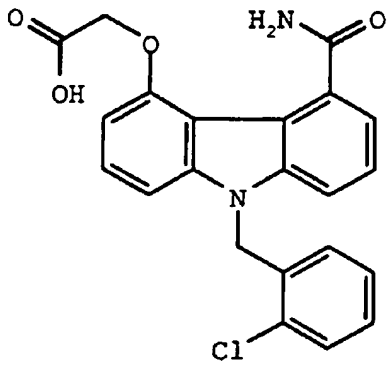
Elemental Analyses for $C_{22}H_{16}N_2O_4INa$,

Calculated: C 50.57; H, 3.07; N, 5.36.

Found: C, 49.57; H, 2.93; N, 5.06.

EXAMPLE 39

Preparation of {9-[(2-Chlorophenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid



A. 9-[(2-Chlorophenyl)methyl]-5-carbomethoxy-1,2-dihydrocarbazol-4(3H)-one

40% Methanolic Triton B (2.42 mL, 5.3 mM) was slowly added dropwise to a solution of 5-carbomethoxy-1,2-dihydro-9H-carbazol-4(3H)-one (873.7 mg, 3.59 mM) in 10 mL of DMF at 25 °C. After 5 minutes, 2-chlorobenzyl bromide (1.11 g, 5.39 mM) was added and the resultant mixture stirred at room temperature for 72 hours. The mixture was diluted with ethyl acetate, washed five times with H_2O, once with saturated brine, dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue was purified by crystallization from ethyl acetate to afford 706.3 mg (53%) of the 9-[(2-chlorophenyl)methyl]-5-carbomethoxy-1,2-dihydrocarbazol-4(3H)-one as a yellow solid. ^1H NMR (DMSO-

d6) δ 7.6 (m, 2H), 7.4-7.1 (m, 4H), 6.5 (d, 1H, J=8 Hz), 5.6 (s, 2H), 3.8 (s, 3H), 2.9 (t, 2H, J=6 Hz), 2.4 (t, 2H, J=6 Hz), and 2.1 (m , 2H). IR ($CHCl_3$, cm^{-1}) 3050, 2950, 1725, 1655, 1462, 1446, 1435, 1288 and 1120. MS (ES) m/e 368, 370.

Elemental Analyses for $C_{21}H_{18}NO_3Cl$:

Calculated: C, 68.57; H, 4.93; N, 3.81.

Found: C, 68.52; H, 5.18; N, 3.67.

B. 9-[(2-Chlorophenyl)methyl]-4-hydroxy-5-carbomethoxy carbazole

A solution of the 9-[(2-chlorophenyl)methyl]-5-carbomethoxy-1,2-dihydrocarbazol-4(3H)-one (692.2 mg, 1.88 mM) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (529 mg, 2.32 mM) in 35 mL of toluene was stirred between 70-80 °C for 6 hours. The mixture was purified directly by column chromatography on silica gel (elution with methylene chloride) to afford 245 mg (35%) of the 9-[(2-chlorophenyl)methyl]-4-hydroxy-5-carbomethyoxy carbazole as a greenish solid. ^1H NMR (DMSO-d6) δ 10.3 (s, 1H), 7.6 (t, 2H, J=8 Hz), 7.4 (t, 1H, J=8 Hz), 7.3-7.1 (m, 4H), 6.9 (d, 1H, J=8 Hz), 6.6 (d, 1H, J=8 Hz), 6.3 (d, 1H, J=8 Hz), 5.65 (s, 2H), and 3.85 (s, 3H). IR ($CHCl_3$, cm^{-1}) 3200 (br), 1686, 1598, 1442, 1428, 1332, 1285, 1267, and 1141. MS (ES) m/e 364, 366, 368.

Elemental Analyses for $C_{21}H_{16}NO_3Cl$:

Calculated: C, 68.95; H, 4.41; N, 3.83.

Found: C, 67.88; H, 4.29; N, 3.67.

C. 9-[(2-Chlorophenyl)methyl]-4-hydroxy-5-carbamoyl carbazole

A solution of the 9-[(2-chlorophenyl)methyl]-4-hydroxy-5-carbomethoxy carbazole (238 mg, 0.43 mM) in 20 mL THF and

25 mL concentrated aqueous ammonium hydroxide was sonicated for 20 hours at 40-50 °C. The mixture was diluted with ethyl acetate and acidified to pH 1 with 5 N HCl. The aqueous layer was extracted twice with ethyl acetate. The combined organic extracts were washed with saturated brine, dried over magnesium sulfate, filtered, and concentrated. The residue was purified by column chromatography on silica gel (elution with gradient methylene chloride/ethyl acetate) to afford 86.9 mg (38%) of the 9-[(2-chlorophenyl)methyl]-4-hydroxy-5-carbamoyl carbazole as a white solid. ^{1}H NMR (DMSO-d6) δ 10.5 (s, 1H), 8.8 (br s, 1H), 8.4 (br s, 1H), 7.7 (m, 1H), 7.55 (d, 1H, J=8 Hz), 7.45 (m, 2H), 7.3 (m, 2H), 7.15 (t, 1H, J=8 Hz), 6.95 (d, 1H, J=8 Hz), 6.6 (d, 1H, J=8 Hz), 6.2 (d, 1H, J=8 Hz), 5.75 (s, 2H). IR ($CHCl_3$, cm^{-1}) 3500, 3400, 3200 (br), 1649, 1597, 1585, 1446, 1431, 1331, and 1269. MS (ES) m/e 349, 351, 353.

Elemental Analyses for $C_{20}H_{15}N_2O_2Cl$:

Calculated: C, 68.48; H, 4.31; N, 7.99.

Found: C, 68.05; H, 4.33; N, 7.19

D. {9-[(2-Chlorophenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, tert-butyl ester

40% Methanolic Triton B (0.15 mL, 0.34 mM) was added to a solution of the 9-[(2-chlorophenyl)methyl]-4-hydroxy-5-carbamoyl carbazole (80 mg, 0.23 mM) in 5 mL DMF at room temperature. After 3 minutes, t-butyl bromoacetate (182 mg, 0.91 mM) was added and the resultant mixture stirred at room temperature for 72 hours. The mixture was diluted with ethyl acetate, washed five times with H_2O, and saturated brine, dried over magnesium sulfate, filtered, and concentrated. The residue was purified by column chromatography on silica gel (elution with ethyl acetate) to afford 57 mg (53%) of the {9-[(2-chlorophenyl)methyl]-5-carbamoylcarbazol-4-

yl}oxyacetic acid, tert-butyl ester as a white solid. ^{1}H NMR (DMSO-d6) δ 7.6 (d, 1H, J=8 Hz), 7.5-6.9 (m, 9H), 6.55 (d, 1H, J=8 Hz), 6.35 (d, 1H, J=8 Hz), 5.7 (s, 2H), 4.75 (s, 2H), and 1.45 (s, 9H). IR (KBr, cm^{-1}) 1753 and 1678. MS (FD) m/e 464.

Elemental Analyses for $C_{26}H_{25}N_2O_4Cl$:

Calculated: C, 67.17; H, 5.42; N, 6.03.

Found: C, 64.02; H, 5.33; N, 5.77.

E. {9-[(2-Chlorophenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid

A solution of the {9-[(2-chlorophenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, tert-butyl ester (46 mg, 0.1 mM) in 3 mL of trifluoroacetic acid was stirred at room temperature for 2 hours. The solvent was removed *in vacuo*. The residue was triturated with diethyl ether/hexanes, then dried *in vacuo* to afford 40 mg (98%) of the {9-[(2-chlorophenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid as a white powder. ^{1}H NMR (DMSO-d6) δ 12.9 (br s, 1H), 7.55 (s, 1H), 7.5 (d, 1H, J=8 Hz), 7.45 (s, 1H), 7.4-7.3 (m, 3H), 7.25 (t, 1H, J=8 Hz), 7.1-7.0 (m, 3H), 6.6 (d, 1H, J=8 Hz), 6.3 (d, 1H, J=8 Hz), 5.7 (s, 2H), and 4.8 (s, 2H). IR (KBr, cm^{-1}) 3430, 1735, and 1635. MS (ES) m/e 407, 409.

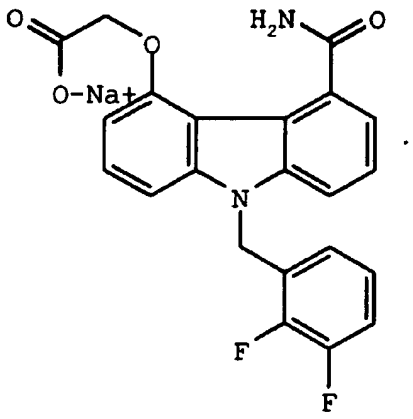
Elemental Analyses for $C_{22}H_{17}N_2O_4Cl$:

Calculated: C, 64.63; H, 4.19; N, 6.85.

Found: C, 64.60; H, 4.08; N, 6.70.

EXAMPLE 40

Preparation of {9-[(2,3-difluorophenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, sodium salt



A. 9-[(2,3-Difluorophenyl)methyl]-5-carbomethoxy-1,2-dihydrocarbazol-4(3H)-one

A suspension of 5-carbomethoxy-1,2-dihydro-9H-carbazol-4(3H)-one (973 mg, 4.0 mM), a-bromo-2,3-difluorotoluene (1.01 g, 4.8 mM), and potassium carbonate (553 mg, 4.0 mM) in 10 mL DMF was stirred at room temperature for 73 hours. The mixture was diluted with ethyl acetate, washed with H_2O, 1 N HCl, H_2O, saturated $NaHCO_3$, H_2O, and saturated brine, dried over anhydrous magnesium sulfate, filtered, concentrated. The residue was purified by column chromatography on silica gel (elution with methylene chloride/ethyl acetate) to afford 1.04 g (70%) of the 9-[(2,3-difluorophenyl)methyl]-5-carbomethoxy-1,2-dihydrocarbazol-4(3H)-one as a tan solid. ^1H NMR ($CDCl_3$) δ 7.4 (d, 1H, J=8 Hz), 7.35 (d, 1H, J=8 Hz), 7.15-6.9 (m, 5H), 6.35 (t, 1H, J=8 Hz), 5.4 (s, 2H), 4.05 (s, 3H), 2.9 (t, 2H, J=6 Hz), 2.6 (t, 2H, J=6 Hz), and 2.25 (m , 2H). IR (KBr, cm^{-1}) 1719 and 1650. MS (ES) m/e 368, 370.

Elemental Analyses for $C_{21}H_{17}NO_3F_2$:

Calculated: C, 68.29; H, 4.64; N, 3.79.

Found: C, 68.50; H, 4.62; N, 3.94.

B. 9-[(2,3-Difluorophenyl)methyl]-4-hydroxy-5-carbomethoxy carbazole

A solution of the 9-[(2,3-difluorophenyl)methyl]-5-carbomethoxy-1,2-dihydrocarbazol-4(3H)-one (490 mg, 1.32 mM) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (336 mg, 1.45 mM) in 70 mL of toluene was stirred at 80-90 °C for 2.25 hours. The mixture was purified directly by column chromatography on silica gel (elution with methylene chloride) to afford 165 mg (34%) of the 9-[(2,3-difluorophenyl)methyl]-4-hydroxy-5-carbomethyoxy carbazole as a yellow solid. ^{1}H NMR ($CDCl_3$) δ 10.25 (s, 1H), 8.0 (d, 1H, J=8 Hz), 7.6 (d, 1H, J=8 Hz), 7.5-7.4 (m, 2H), 7.05 (m, 1H), 6.9 (d, 1H, J=8 Hz), 6.85 (d, 1H, J=8 Hz), 6.8 (m, 1H), 6.35 (t, 1H, J=8 Hz), 5.6 (s, 2H), and 4.1 (s, 3H). IR (KBr, cm^{-1}) 3025 and 1684. MS (ES) m/e 366, 368.

Elemental Analyses for $C_{21}H_{15}NO_3F_2$:

Calculated: C, 68.66; H, 4.12; N, 3.81.

Found: C, 69.54; H, 4.44; N, 3.81.

C. 9-[(2,3-Difluorophenyl)methyl]-4-hydroxy-5-carbamoyl carbazole

A solution of the 9-[(2,3-difluorophenyl)methyl]-4-hydroxy-5-carbomethoxy carbazole (514 mg, 1.4 mM) in 5 mL THF and 20 mL concentrated aqueous ammonium hydroxide was stirred at room temperature for 94 hours. The mixture was diluted with ethyl acetate and acidified to pH 1 with 5 N HCl. The aqueous layer was extracted three times with ethyl acetate. The combined organic extracts were washed with H_2O and saturated brine, dried over magnesium sulfate, filtered, and concentrated. The residue was purified by column chromatography on silica gel (elution with gradient

hexanes/ethyl acetate) to afford 320 mg (65%) of the 9-[(2,3-difluorophenyl)methyl]-4-hydroxy-5-carbamoyl carbazole as a yellow solid. ^{1}H NMR (DMSO-d6) δ 10.45 (s, 1H), 8.8 (br s, 1H), 8.4 (br s, 1H), 7.8 (d, 1H, J=8 Hz), 7.5- 7.2 (m, 4H), 7.05 (d, 1H, J=8 Hz), 6.95 (m, 1H), 6.6 (d, 1H, J=8 Hz), 6.35 (t, 1H, J=8 Hz), and 5.9 (s, 2H). IR (KBr, cm^{-1}) 3350, 3125, 1628, 1598, and 1583. MS (ES) m/e 351, 353.

Elemental Analyses for $C_{20}H_{14}N_2O_2F_2$:

Calculated: C, 68.18; H, 4.01; N, 7.95.

Found: C, 68.15; H, 4.23; N, 8.01.

D. {9-[(2,3-Difluorophenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, methyl ester

40% Methanolic Triton B (0.51 mL, 1.12 mM) was added to a solution of the 9-[(2,3-difluorophenyl)methyl]-4-hydroxy-5-carbamoyl carbazole (303 mg, 0.86 mM) in 5 mL DMF at room temperature. After 15 minutes, methyl bromoacetate (270 mg, 1.72 mM) was added and the resultant mixture stirred at room temperature for 18 hours. The mixture was diluted with ethyl acetate, washed with H_2O, 1 N HCl, H_2O, and saturated brine, dried over magnesium sulfate, filtered, and concentrated. The residue was purified by column chromatography on silica gel (elution with ethyl acetate) to afford 295 mg (80%) of the {9-[(2,3-difluorophenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, methyl ester as a white solid. ^{1}H NMR ($CDCl_3$) δ 7.5-7.3 (m, 5H), 7.05 (d, 1H, J=8 Hz), 6.8 (m, 1H), 6.6 (d, 1H, J=8 Hz), 6.4 (t, 1H, J=8 Hz), 6.2 (br s, 1H), 6.0 (br s, 1H), 5.6 (s, 2H), 4.9 (s, 2H), and 3.8 (s, 3H). IR (KBr, cm^{-1}) 3432, 3180, 1774, 1766,and 1674. MS (ES) m/e 425.

Elemental Analyses for $C_{23}H_{18}N_2O_4F_2$:

Calculated: C, 65.09; H, 4.28; N, 6.60.

Found: C, 64.11; H, 4.12; N, 6.32.

E. {9-[(2,3-Difluorophenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, sodium salt

A suspension of the {9-[(2,3-difluorophenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, methyl ester (85 mg, 0.2 mM) and 0.22 mL (0.22 mM) of 1 N NaOH in 5 mL of ethanol was stirred for 18 hours at 25 °C. A small volume of diethyl ether/hexanes was added, then cooled in the refrigerator. The resultant white precipitate was collected by filtration, washed with a small amount of EtOH/diethyl ether/hexanes , then dried *in vacuo* to afford 77 mg (89%) of the {9-[(2,3-difluorophenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, sodium salt as a white powder. ^{1}H NMR (DMSO-d6) δ 7.7-7.2 (m, 6H), 7.2-7.0 (m, 3H), 6.6 (d, 1H, J=8 Hz), 6.45 (t, 1H, J=8 Hz), 5.7 (s, 2H), and 4.35 (s, 2H). IR (KBr, cm^{-1}) 3467, 3390, 1662, and 1616. MS (ES) m/e 409, 411, 433.

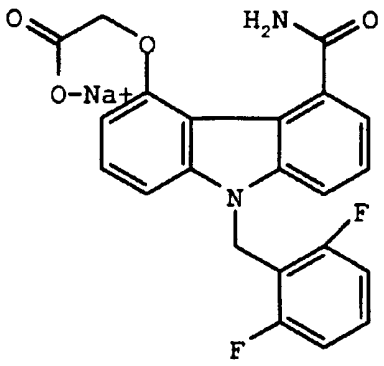
Elemental Analyses for $C_{22}H_{15}N_2O_4F_2Na$:

Calculated: C, 61.12; H, 3.50; N, 6.48.

Found: C, 61.34; H, 3.38; N, 6.41.

EXAMPLE 41

Preparation of {9-[(2,6-difluorophenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, sodium salt



A. 9-[(2,6-Difluorophenyl)methyl]-5-carbomethoxy-1,2-dihydrocarbazol-4(3H)-one

A suspension of 5-carbomethoxy-1,2-dihydro-9H-carbazol-4(3H)-one (973 mg, 4.0 mM), a-bromo-2,6-difluorotoluene (1.01 g, 4.8 mM), and potassium carbonate (553 mg, 4.0 mM) in 10 mL DMF was stirred at room temperature for 74 hours. The mixture was diluted with ethyl acetate, washed with H_2O, 1 N HCl, H_2O, saturated $NaHCO_3$, H_2O, and saturated brine, dried over anhydrous magnesium sulfate, filtered, concentrated. The residue was purified by column chromatography on silica gel (elution with methylene chloride/ethyl acetate) to afford 1.04 g (70%) of the 9-[(2,6-difluorophenyl)methyl]-5-carbomethoxy-1,2-dihydrocarbazol-4(3H)-one as a tan solid. ^1H NMR ($CDCl_3$) δ 7.5 (d, 1H, J=8 Hz), 7.35-7.2 (m, 3H), 6.95 (t, 2H, J=8 Hz), 5.4 (s, 2H), 4.0 (s, 3H), 3.05 (t, 2H, J=6 Hz), 2.6 (t, 2H, J=6 Hz), and 2.25 (m, 2H). IR (KBr, cm^{-1}) 1728 and 1655. MS (ES) m/e 370.

Elemental Analyses for $C_{21}H_{17}NO_3F_2$:

Calculated: C, 68.29; H, 4.64; N, 3.79.
Found: C, 68.51; H, 4.82; N, 3.78.

B. 9-[(2,6-Difluorophenyl)methyl]-4-hydroxy-5-carbomethoxy carbazole

A 60% oil dispersion of sodium hydride (257 mg, 6.42 mM) was added to a solution of the 9-[(2,6-difluorophenyl)methyl]-5-carbomethoxy-1,2-dihydrocarbazol-4(3H)-one (1.03 g, 2.79 mM) in 7 mL of dioxane at room temperature. After 5 minutes methyl benzenesulfinate (0.6 mL, 4.46 mM) was added and the mixture stirred at room temperature for 1.75 hours. The mixture was diluted with 10 mL dioxane, then glacial acetic acid (0.37 mL, 6.42 mM) was added. The resultant mixture was refluxed for 45 min, cooled

to room temperature, diluted with ethyl acetate, washed three times with saturated $NaHCO_3$, and saturated brine, dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was purified by column chromatography on silica gel (elution with toluene) to afford 480 mg (47%) of the 9-[(2,6-difluorophenyl)methyl]-4-hydroxy-5-carbomethyoxy carbazole as a yellow solid. ^1H NMR ($CDCl_3$) δ 10.15 (s, 1H), 7.95 (d, 1H, J=8 Hz), 7.5 (d, 1H, J=8 Hz), 7.5-7.0 (m, 4H), 6.9-6.8 (m, 3H), 5.6 (s, 2H), and 4.1 (s, 3H). IR (KBr, cm^{-1}) 3040 and 1682. MS (ES) m/e 366, 368.

Elemental Analyses for $C_{21}H_{15}NO_3F_2$:

Calculated: C, 68.66; H, 4.12; N, 3.81.

Found: C, 69.48; H, 4.07; N, 4.11.

C. 9-[(2,6-Difluorophenyl)methyl]-4-hydroxy-5-carbamoyl carbazole

A solution of the 9-[(2,6-difluorophenyl)methyl]-4-hydroxy-5-carbomethoxy carbazole (514 mg, 1.4 mM) in 5 mL THF and 20 mL concentrated aqueous ammonium hydroxide was stirred at room temperature for 64 hours. The pH was adjusted to 10.5 with 5 N HCl. The resultant precipitate was collected by filtration, resuspended in H_2O, adjusted the pH to 11.7 with concentrated ammonium hydroxide. The resultant precipitate was collected by filtration. The precipitate was dissolved in ethyl acetate, washed three times with 5 N NaOH, H_2O, and saturated brine, dried over anhydrous magnesium sulfate, filtered, concentrated to afford 310 mg (70%) of the 9-[(2,6-difluorophenyl)methyl]-4-hydroxy-5-carbamoyl carbazole as a yellow solid. ^1H NMR (DMSO-d6) δ 10.4 (s, 1H), 8.8 (br s, 1H), 8.4 (br s, 1H), 7.8 (d, 1H, J=8 Hz), 7.6-7.0 (m, 7H), 6.6 (d, 1H, J=8 Hz), and 5.7 (s,

2H). IR (KBr, cm^{-1}) 3404, 3113, 1626, and 1587. MS (ES) m/e 351, 353.

Elemental Analyses for $C_{20}H_{14}N_2O_2F_2$:

Calculated: C, 68.18; H, 4.01; N, 7.95.

Found: C, 68.45; H, 4.01; N, 7.87.

D. {9-[(2,6-Difluorophenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, methyl ester

40% Methanolic Triton B (0.49 mL, 1.07 mM) was added to a solution of the 9-[(2,6-difluorophenyl)methyl]-4-hydroxy-5-carbamoyl carbazole (290 mg, 0.82 mM) in 5 mL DMF at room temperature. After 15 minutes, methyl bromoacetate (259 mg, 1.65 mM) was added and the resultant mixture stirred at room temperature for 24 hours. The mixture was diluted with H_2O and the resultant white precipitate collected by filtration, triturated with diethyl ether/hexanes, and dried *in vacuo* to afford 228 mg (65%) of the {9-[(2,6-difluorophenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, methyl ester as a white solid. ^1H NMR ($CDCl_3$) δ 7.65 (d, 1H, J=8 Hz), 7.45-7.2 (m, 5H), 6.85 (t, 2H, J=8 Hz), 6.55 (d, 1H, J=8 Hz), 6.3 (br s, 1H), 6.0 (br s, 1H), 5.5 (s, 2H), 4.9 (s, 2H), and 3.8 (s, 3H). IR (KBr, cm^{-1}) 3432, 3170, 1762, and 1675. MS (ES) m/e 425.

Elemental Analyses for $C_{23}H_{16}N_2O_4F_2$:

Calculated: C, 65.09; H, 4.28; N, 6.60.

Found: C, 65.05; H, 4.40; N, 6.53.

E. {9-[(2,6-Difluorophenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, sodium salt

A suspension of the {9-[(2,6-difluorophenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, methyl ester (85 mg, 0.2 mM) and 0.22 mL (0.22 mM) of 1 N NaOH in 5 mL of ethanol

was stirred for 18 hours at 25 °C. A small volume of diethyl ether/hexanes was added, then cooled in the refrigerator. The resultant white precipitate was collected by filtration, washed with a small amount of EtOH/diethyl ether/hexanes , then dried *in vacuo* to afford 82 mg (95%) of the {9-[(2,6-difluorophenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, sodium salt as a white powder. ^{1}H NMR (DMSO-d6) δ 7.6 (d, 1H, J=8 Hz), 7.55 (br s, 1H), 7.45-7.3 (m, 3H), 7.25 (t, 1H, J=8 Hz), 7.1-7.0 (m, 4H), 6.5 (d, 1H, J=8 Hz), 5.65 (s, 2H), and 4.3 (s, 2H). IR (KBr, cm^{-1}) 3470, 3360, 1658, and 1606. MS (ES) m/e 409, 411, 433.

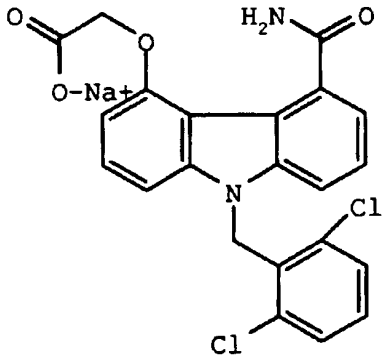
Elemental Analyses for $C_{22}H_{15}N_2O_4F_2Na$:

Calculated: C, 61.12; H, 3.50; N, 6.48.

Found: C, 59.18; H, 3.70; N, 6.19.

EXAMPLE 42

Preparation of {9-[(2,6-dichlorophenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, sodium salt



A. 9-[(2,6-Dichlorophenyl)methyl]-5-carbomethoxy-1,2-dihydrocarbazol-4(3H)-one

A suspension of 5-carbomethoxy-1,2-dihydro-9H-carbazol-4(3H)-one (973 mg, 4.0 mM), a-bromo-2,6-dichlorotoluene (1.19 g, 4.8 mM), and potassium carbonate (553 mg, 4.0 mM) in 10 mL DMF was stirred at room temperature for 24 hours.

The mixture was diluted with ethyl acetate, washed with H_2O, 1 N HCl, H_2O, saturated $NaHCO_3$, H_2O, and saturated brine, dried over anhydrous magnesium sulfate, filtered, concentrated. The residue was purified by column chromatography on silica gel (elution with methylene chloride/ethyl acetate) to afford 900 mg (56%) of the 9-[(2,6-dichlorophenyl)methyl]-5-carbomethoxy-1,2-dihydrocarbazol-4(3H)-one as a white foam. ^1H NMR ($CDCl_3$) δ 7.4-7.2 (m, 6H), 5.6 (s, 2H), 4.0 (s, 3H), 2.9 (t, 2H, J=6 Hz), 2.55 (t, 2H, J=6 Hz), and 2.2 (m, 2H). IR (KBr, cm^{-1}) 1725 and 1652. MS (ES) m/e 400, 402, 404.

Elemental Analyses for $C_{21}H_{17}NO_3Cl_2$:

Calculated: C, 62.70; H, 4.26; N, 3.48.

Found: C, 62.98; H, 4.35; N, 3.35.

B. 9-[(2,6-Dichlorophenyl)methyl]-4-hydroxy-5-carbomethoxy carbazole

A solution of the 9-[(2,6-dichlorophenyl)methyl]-5-carbomethoxy-1,2-dihydrocarbazol-4(3H)-one (861 mg, 2.14 mM) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (595 mg, 2.57 mM) in 60 mL of toluene was stirred at reflux for 3.5 hours. The mixture was purified directly by column chromatography on silica gel (elution with methylene chloride) to afford 255 mg (29%) of the 9-[(2,6-dichlorophenyl)methyl]-4-hydroxy-5-carbomethyoxy carbazole as a yellow solid. ^1H NMR ($CDCl_3$) δ 10.05 (s, 1H), 7.95 (d, 1H, J=8 Hz), 7.6 (d, 1H, J=8 Hz), 7.45-7.2 (m, 5H), 6.95 (d, 1H, J=8 Hz), 6.8 (d, 1H, J=8 Hz), 5.75 (s, 2H), and 4.1 (s, 3H). IR (KBr, cm^{-1}) 3430 and 1668. MS (ES) m/e 409, 411.

Elemental Analyses for $C_{21}H_{15}NO_3Cl_2$:

Calculated: C, 63.02; H, 3.78; N, 3.50.

Found: C, 63.78; H, 3.82; N, 3.59.

C. 9-[(2,6-Dichlorophenyl)methyl]-4-hydroxy-5-carbamoyl carbazole

A solution of the 9-[(2,6-dichlorophenyl)methyl]-4-hydroxy-5-carbomethoxy carbazole (240 mg, 0.6 mM) in 5 mL THF and 20 mL concentrated aqueous ammonium hydroxide was stirred at room temperature for 22 hours. The resultant precipitate was collected by filtration and dried *in vacuo* to afford 151 mg (65%) of the 9-[(2,6-dichlorophenyl)methyl]-4-hydroxy-5-carbamoyl carbazole as a yellow solid. ^{1}H NMR (DMSO-d6) δ 10.35 (s, 1H), 8.8 (br s, 1H), 8.4 (br s, 1H), 7.7 (d, 1H, J=8 Hz), 7.6-7.3 (m, 5H), 7.25 (t, 1H, J=8 Hz), 6.85 (d, 1H, J=8 Hz), 6.55 (d, 1H, J=8 Hz), and 5.85 (s, 2H). IR (KBr, cm^{-1}) 3429, 1631, and 1597. MS (ES) m/e 385, 387.

Elemental Analyses for $C_{20}H_{14}N_2O_2Cl_2$:

Calculated:	C, 62.35; H, 3.66; N, 7.27.
Found:	C, 62.87; H, 3.99; N, 6.00.

D. {9-[(2,6-Dichlorophenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, methyl ester

40% Methanolic Triton B (0.23 mL, 0.49 mM) was added to a solution of the 9-[(2,6-dichlorophenyl)methyl]-4-hydroxy-5-carbamoyl carbazole (146 mg, 0.38 mM) in 5 mL DMF at room temperature. After 15 minutes, methyl bromoacetate (119 mg, 0.76 mM) was added and the resultant mixture stirred at room temperature for 17 hours. The mixture was diluted with ethyl acetate, washed with H_2O, 1 N HCl, H_2O, sat. $NaHCO_3$, and saturated brine, dried over magnesium sulfate, filtered, and concentrated. The residue was purified by column chromatography on silica gel (elution with ethyl acetate) to afford 83 mg (48%) of the {9-[(2,6-dichlorophenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, methyl ester as a tan solid. ^{1}H NMR (DMSO-d6) δ 7.5-7.0 (m, 10H), 6.55 (d, 1H,

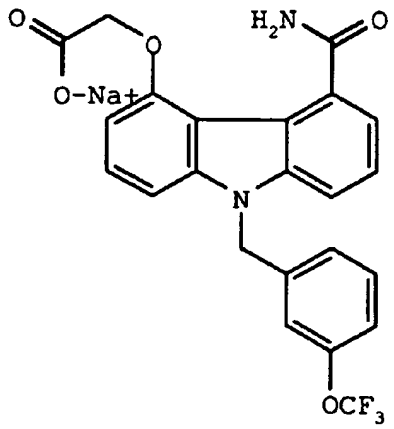
J=8 Hz), 5.8 (s, 2H), 4.9 (s, 2H), and 3.75 (s, 3H). IR (KBr, cm^{-1}) . MS (ES) m/e 457, 459.

E. {9-[(2,6-Dichlorophenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, sodium salt

A suspension of the {9-[(2,6-dichlorophenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, methyl ester (45.7 mg, 0.1 mM) and 0.11 mL (0.11 mM) of 1 N NaOH in 5 mL of ethanol was stirred for 22 hours at 25 °C. A small volume of diethyl ether/hexanes was added, then cooled in the refrigerator. The resultant white precipitate was collected by filtration, washed with a small amount of EtOH/diethyl ether/hexanes , then dried *in vacuo* to afford 40 mg (86%) of the {9-[(2,6-dichlorophenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, sodium salt as a white powder. ^{1}H NMR (DMSO-d6) δ 7.6-7.4 (m, 6H), 7.3 (t, 1H, J=8 Hz), 7.2 (t, 1H, J=8 Hz), 7.0 (d, 1H, J=8 Hz), 6.9 (t, 1H, J=8 Hz), 6.5 (d, 1H, J=8 Hz), 5.8 (s, 2H), and 4.25 (s, 2H). MS (ES) m/e 441, 443, 445.

EXAMPLE 43

Preparation of {9-[(3-trifluoromethoxyphenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, sodium salt



A. 9-[(3-Trifluoromethoxyphenyl)methyl]-5-carbomethoxy-1,2-dihydrocarbazol-4(3H)-one

A suspension of 5-carbomethoxy-1,2-dihydro-9H-carbazol-4(3H)-one (935 mg, 3.85 mM), 3-trifluoromethoxybenzyl bromide (1.0 g, 3.93 mM), and potassium carbonate (531 mg, 3.85 mM) in 20 mL DMF was stirred at room temperature for 17 hours. The mixture was diluted with ethyl acetate, washed with H_2O and saturated brine, dried over anhydrous magnesium sulfate, filtered, concentrated to afford 1.6 g (100%) of the 9-[(3-trifluoromethoxyphenyl)methyl]-5-carbomethoxy-1,2-dihydrocarbazol-4(3H)-one as a foam. ^{1}H NMR (DMSO-d6) δ 7.7 (dd, 1H, J=1 and 8 Hz), 7.45 (t, 1H, J=8 Hz), 7.3-7.1 (m, 4H), 7.05 (d, 1H, J=8 Hz), 5.6 (s, 2H), 3.8 (s, 3H), 3.0 (m, 2H), 2.45 (m, 2H), and 2.1 (m, 2H). IR ($CHCl_3$, cm^{-1}) 1729, 1647, 1439, 1259, 1176, and 1116. MS (ES) m/e 418.

Elemental Analyses for $C_{22}H_{18}NO_4F_3$:

Calculated:	C, 63.31; H, 4.32; N, 3.36.
Found:	C, 63.12; H, 4.35; N, 3.31.

B. 9-[(3-Trifluoromethoxyphenyl)methyl]-4-hydroxy-5-carbomethoxy carbazole

A solution of the 9-[(3-trifluoromethoxyphenyl)methyl]-5-carbomethoxy-1,2-dihydrocarbazol-4(3H)-one (0.75 g, 1.8 mM) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (490 mg, 2.16 mM) in 70 mL of toluene was stirred at reflux for 6 hours. The mixture was purified directly by column chromatography on silica gel (elution with methylene chloride) to afford 300 mg (40%) of the 9-[(3-trifluoromethoxyphenyl)methyl]-4-hydroxy-5-carbomethyoxy carbazole as a yellow solid. ^{1}H NMR (DMSO-d6) δ 10.25 (s, 1H), 7.7 (d, 1H, J=8 Hz), 7.5-7.0 (m, 8H), 6.6 (d, 1H, J=8 Hz), 5.7 (s, 2H), and 3.85 (s, 3H). IR (KBr, cm^{-1}) 3200, 1673, 1441, 1268, 1217, 1173, and 753. MS (ES) m/e 414, 416.

Elemental Analyses for $C_{22}H_{16}NO_3F_3$

Calculated: C, 63.61; H, 3.86; N, 3.37.

Found: C, 63.40; H, 3.99; N, 3.43.

C. 9-[(3-Trifluoromethoxyphenyl)methyl]-4-hydroxy-5-carbamoyl carbazole

A solution of the 9-[(3-trifluoromethoxyphenyl)methyl]-4-hydroxy-5-carbomethoxy carbazole (260 mg, 0.62 mM) in 10 mL THF and 30 mL concentrated aqueous ammonium hydroxide was stirred vigorously for 132 hours. The mixture was diluted with ethyl acetate and acidified to pH 1 with 5 N HCl. The aqueous layer was extracted three times with ethyl acetate. The combined organic extracts were washed with H_2O and saturated brine, dried over magnesium sulfate, filtered, and concentrated. The residue was purified by column chromatography on silica gel (elution with gradient hexanes/ethyl acetate) to afford 150 mg (60%) of the 9-[(3-trifluoromethoxyphenyl)methyl]-4-hydroxy-5-carbamoyl carbazole as an off-white solid. ^1H NMR (DMSO-d6) δ 10.5 (s, 1H), 8.8 (br s, 1H), 8.4 (br s, 1H), 7.85 (dd, 1H, J=1 and 8 Hz), 7.5-7.15 (m, 5H), 7.1 (d, 1H, J=8 Hz), 7.0 (d, 1H, J=8 Hz), 6.6 (d, 1H, J=8 Hz), 5.95 (d, 1H, J=8 Hz), and 5.65 (s, 2H). IR (KBr, cm^{-1}) 3431, 3203, 1629, 1601, 1580, 1548, 1446, 1330, 1261, 1215, and 777. MS (ES) m/e 399, 401.

Elemental Analyses for $C_{21}H_{15}N_2O_2F_3$:

Calculated: C, 63.00; H, 3.75; N, 7.0.

Found: C, 63.15; H, 4.07; N, 6.84.

D. {9-[(3-Trifluoromethoxyphenyl)methyl]-5-carbamoylcarbazol-4-yl)oxyacetic acid, methyl ester

40% Methanolic Triton B (0.15 mL, 0.34 mM) was added to a solution of the 9-[(3-trifluoromethoxyphenyl)methyl]-4-hydroxy-5-carbamoyl carbazole (115 mg, 0.28 mM) in 8 mL DMF

at room temperature. After 3 minutes, methyl bromoacetate (65 mg, 0.41 mM) was added and the resultant mixture stirred at room temperature for 23 hours. The mixture was diluted with ethyl acetate, washed with H_2O, and saturated brine, dried over magnesium sulfate, filtered, and concentrated. The residue was purified by column chromatography on silica gel (elution with ethyl acetate) to afford 112 mg (83%) of the {9-[(3-trifluoromethoxyphenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, methyl ester as a white solid. ^{1}H NMR (DMSO-d6) δ 7.6 (d, 1H, J=8 Hz), 7.55 (br s, 1H), 7.5-7.0 (m, 9H), 6.6 (d, 1H, J=8 Hz), 5.7 (s, 2H), 4.9 (s, 2H), and 3.75 (s, 3H). IR (KBr, cm^{-1}) 3488, 3141, 1763, 1674, 1501, 1444, 1269, 1215, 1178, 1102, 772, and 714. MS (FD) m/e 472.

Elemental Analyses for $C_{24}H_{19}N_2O_5F_3$:

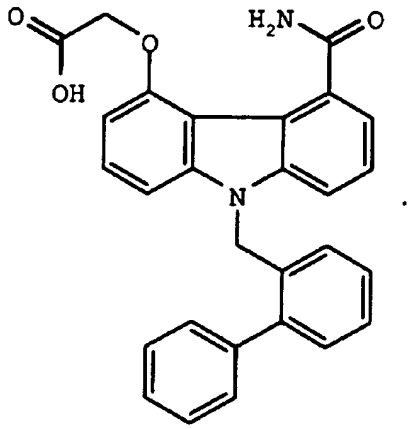
Calculated: C, 61.02; H, 4.03; N, 5.93.

Found: C, 61.05; H, 4.17; N, 5.81.

E. {9-[(3-Trifluoromethoxyphenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, sodium salt

A suspension of the {9-[(3-trifluoromethoxyphenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, methyl ester (22.4 mg, 0.047 mM) and 0.065 mL (0.065 mM) of 1 N NaOH in 5 mL of ethanol was stirred for 24 hours at 25 °C. The solvent was removed *in vacuo* and the residue suspended in EtOH. The resultant white precipitate was collected by filtration, washed with a small amount of EtOH, then dried *in vacuo* to afford 9 mg (41%) of the {9-[(3-trifluoromethoxyphenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, sodium salt as a white powder. MS (ES) m/e 457, 459.

EXAMPLE 44 Preparation of (9-[(2-biphenyl)methyl]-5-carbamoylcarbazol-4-yl)oxyacetic acid



A. 2-Carbomethoxy-6-nitro-2'-methoxy-biphenyl

A solution of methyl 2-chloro-3-nitrobenzoate (2.16 g, 10.0 mM), 2-methoxybenzeneboronic acid (1.64g, 10.5 mM), tetrakis(triphenylphosphine)palladium (0) (584 mg, 0.5 mM), and 2 M aqueous sodium carbonate (10.5 mL, 21.0 mM) in 50 mL of THF was wrapped in aluminum foil and stirred at reflux for 27 hours. The THF was removed *in vacuo* and the residue dissolved in ethyl acetate. The mixture was washed with with H_2O, 1 N HCl, H_2O, sat. $NaHCO_3$, and saturated brine, dried over magnesium sulfate, filtered, and concentrated. The resultant light brown oil was purified by column chromatography on silica (elution with gradient toluene/ethyl acetate) to afford 2.0 g (69%) of 2-carbomethoxy-6-nitro-2'-methoxy-biphenyl as a yellow-orange solid. ^1H NMR ($CDCl_3$) δ 8.05 (d, 1H, J=8 Hz), 7.95 (d, 1H, J=8 Hz), 7.55 (t, 1H, J=8 Hz), 7.35 (t, 1H, J=8 Hz), 7.05 (d, 1H, J=8 Hz), 7.0 (t, 1H, J=8 Hz), 6.9 (d, 1H, J=8 Hz), 3.7 (s, 3H), and 3.6 (s, 3H). IR (KBr, cm^{-1}) 1730, 1538, 1499, 1366, 1298, 1271, 1130, 774, 765, 759, 752, and 707. MS (ES) m/e 288.

Elemental Analyses for $C_{15}H_{13}NO_5$:

Calculated: C, 62.72; H, 4.56; N, 4.88.
Found: C, 62.65; H, 4.61; N, 4.72.

B. 9H-4-methoxy-5-carbomethoxy carbazole

A solution of the 2-carbomethoxy-6-nitro-2'-methoxy-biphenyl (144 mg, 0.5 mM) in triethylphosphite (339 mg, 0.35 mL, 2.0 mM) was heated at 150-160 °C in a sealed tube for 4 h then at room temperature for 15 hours. The mixture was dried *in vacuo* with toluene, then purified by preparative TLC on silica gel (elution with 4:1 toluene/ethyl acetate to afford 39.0 mg (30%) of the 9H-4-methoxy-5-carbomethoxy carbazole as a tan solid. ^{1}H NMR ($CDCl_3$) δ 8.25 (s, 1H), 7.4-7.2 (m, 4H), 7.05 (d, 1H, J=8 Hz), 6.65 (d, 1H, J=8 Hz), and 4.05 (s, 6H). IR ($CHCl_3$, cm^{-1}) 3274 (br), 1706, 1602, 1583, 1456, 1431, 1351, 1333, 1294, 1239, 1198, 1175, 1144, 1103, 781, and 724. MS (ES) m/e 256.

Elemental Analyses for $C_{15}H_{13}NO_3$:
Calculated: C, 70.58; H, 5.13; N, 5.49.
Found: C, 70.85; H, 5.29; N, 5.29.

C. 9-[(2-Biphenyl)methyl]-4-methoxy-5-carbomethoxy carbazole

A solution of the 9H-4-methoxy-5-carbomethoxy carbazole (727 mg, 2.85 mM) in 15 mL DMF was added to 60% NaH mineral oil dispersion (342 mg, 8.56 mM, washed twice with hexane) at room temperature. Following cessation of gas evolution, 2-(bromomethyl)biphenyl (0.79 mL, 4.19 mM) was added and the mixture stirred at room temperature for 19 hours. The mixture was diluted with ethyl acetate and H_2O. The ethyl acetate layer was washed with with H_2O, 1 N HCl, H_2O, sat. $NaHCO_3$, and saturated brine, dried over magnesium sulfate, filtered, and concentrated to afford 1.2 g (100%) of the 9-[(2-biphenyl)methyl]-4-methoxy-5-carbomethoxy carbazole as a

yellow solid. ^{1}H NMR ($CDCl_3$) δ 7.6-7.2 (m, 11H), 7.05 (t, 1H, J=8 Hz), 6.8 (d, 1H, J=8 Hz), 6.65 (d, 1H, J=8 Hz), 6.6 (d, 1H, J=8 Hz), 5.4 (s, 2H) and 4.0 (s, 6H). IR (KBr, cm^{-1}) 1727. MS (ES) m/e 422.

Elemental Analyses for $C_{28}H_{23}NO_3$:

Calculated: C, 79.79; H, 5.50; N, 3.32.
Found: C, 79.53; H, 5.61; N, 3.15.

D. 9-[(2-Biphenyl)methyl]-4-hydroxy-5-carbomethoxy carbazole

Boron tribromide (1.0 M in methylene chloride, 1.69 mL, 1.69 mM) was slowly added to a solution of 9-[(2-biphenyl)methyl]-4-methoxy-5-carbomethoxy carbazole (547 mg, 1.3 mM) in 5 mL methylene chloride at -10 °C. After 2 hours, the mixture was quenched with methanol (1.31 mL, 32.5 mM) and stirred at room temperature for 5 hours. The mixture was diluted with ethyl acetate, washed with H_2O, 1 N HCl, H_2O, sat. $NaHCO_3$, and saturated brine, dried over magnesium sulfate, filtered, and concentrated. The residue was purified by column chromatography on silica gel (elution with methylene chloride) to afford 445 mg (84%) of the 9-[(2-biphenyl)methyl]-4-hydroxy-5-carbomethoxy carbazole as a yellow foam. ^{1}H NMR ($CDCl_3$) δ 10.35 (s, 1H), 7.95 (d, 1H, J=8 Hz), 7.6-7.2 (m, 10fH), 7.05 (t, 1H, J=8 Hz), 6.8 (m, 2H), 6.6 (d, 1H, J=8 Hz), 5.4 (s, 2H), and 4.1 (s, 3H). IR (KBr, cm^{-1}) 3200 (br), 1680, 1596, 1451, 1439, 1427, 1333, 1262, 1217, 1137, 752, 713, 1763 and 703. MS (ES) m/e 406, 408.

Elemental Analyses for $C_{27}H_{21}NO_3$:

Calculated: C, 79.59; H, 5.19; N, 3.44.
Found: C, 80.62; H, 5.73; N, 3.44.

E. 9-[(2-Biphenyl)methyl]-4-hydroxy-5-carbamoyl carbazole

A solution of the 9-[(2-biphenyl)methyl]-4-hydroxy-5-carbomethoxy carbazole (407.5 mg, 1.0 mM) in 5 mL THF and 20 mL concentrated aqueous ammonium hydroxide was sonicated for 28.5 hours at 40-50 °C. The mixture was diluted with ethyl acetate and acidified to pH 1 with 5 N HCl. The aqueous layer was extracted three times with ethyl acetate. The combined organic extracts were washed with H_2O and saturated brine, dried over magnesium sulfate, filtered, and concentrated. The residue was purified by column chromatography on silica gel (elution with gradient methylene chloride/ethyl acetate) to afford 165 mg (42%) of the 9-[(2-biphenyl)methyl]-4-hydroxy-5-carbamoyl carbazole as a yellow solid. ^{1}H NMR (DMSO-d6) δ 10.45 (s, 1H), 8.8 (br s, 1H), 8.4 (br s, 1H), 7.6-7.2 (m, 11H), 7.05 (t, 1H, J=8 Hz), 6.75 (d, 1H, J=8 Hz), 6.55 (d, 1H, J=8 Hz), 6.35 (d, 1H, J=8 Hz), and 5.55 (s, 2H). IR (KBr, cm^{-1}) 3451, 3331, and 1639. MS (ES) m/e 391, 393.

Elemental Analyses for $C_{26}H_{20}N_2O_2$:

Calculated: C, 79.57; H, 5.14; N, 7.14.

Found: C, 79.60; H, 5.37; N, 6.90.

F. {9-[(2-Biphenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, tert-butyl ester

40% Methanolic Triton B (0.2 mL, 0.44 mM) was added to a solution of the 9-[(2-biphenyl)methyl]-4-hydroxy-5-carbamoyl carbazole (141 mg, 0.36 mM) in 5 mL DMF at room temperature. After 5 minutes, t-butyl bromoacetate (107 mg, 0.54 mM) was added and the resultant mixture stirred at room temperature for 6.5 hours. The mixture was diluted with ethyl acetate, washed with H_2O, 1 N HCl, H_2O, sat. $NaHCO_3$, and saturated brine, dried over magnesium sulfate, filtered, and concentrated. The residue was purified by column

chromatography on silica gel (elution with gradient methylene chloride/ethyl acetate) to afford 140 mg (76%) of the {9-[(2-biphenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, tert-butyl ester as a white foam. ^{1}H NMR ($CDCl_3$) δ 7.6-7.2 (m, 13H), 7.05 (t, 1H, J=8 Hz), 6.85 (d, 1H, J=8 Hz), 6.6 (d, 1H, J=8 Hz), 6.55 (d, 1H, J=8 Hz), 5.4 (s, 2H), 4.8 (s, 2H), and 1.45 (s, 9H). IR ($CHCl_3$, cm^{-1}) 1753 and 1674. MS (ES) m/e 507.

Elemental Analyses for $C_{32}H_{30}N_2O_4$:

Calculated: C, 75.87; H, 5.97; N, 5.53.
Found: C, 76.10; H, 6.12; N, 5.37.

G. {9-[(2-Biphenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid

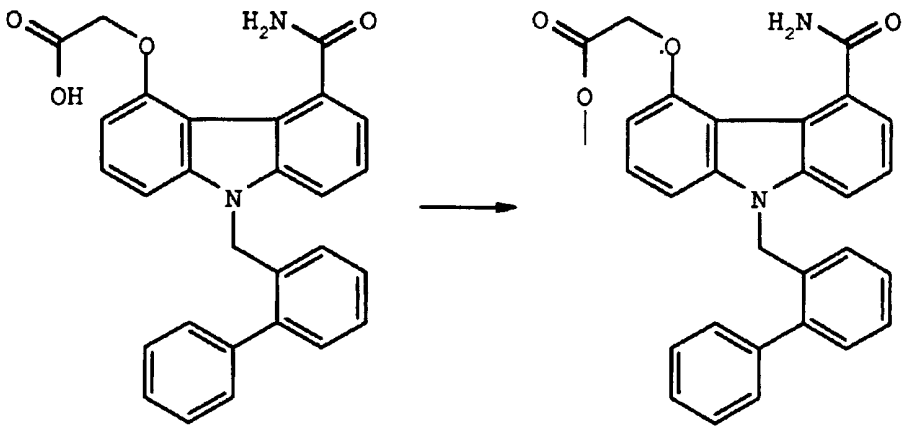
A solution of the {9-[(2-biphenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, tert-butyl ester (116 mg, 0.23 mM) in 3 mL of trifluoroacetic acid was stirred at room temperature for 2 hours. The solvent was removed *in vacuo*. The residue was triturated with ethyl ether/hexanes, then dried *in vacuo* to afford 103 mg (100%) of the {9-[(2-biphenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid as a white powder. ^{1}H NMR (DMSO-d6) δ 12.95 (br s, 1H), 7.75 (s, 1H), 7.65 (d, 2H, J=8 Hz), 7.55 (t, 2H, J=8 Hz), 7.4 (s, 1H), 7.35-7.2 (m, 6H), 7.05 (m, 2H), 6.9 (d, 1H, J=8 Hz), 6.6 (d, 1H, J=8 Hz), 6.4 (d, 1H, J=8 Hz), 5.55 (s, 2H), and 4.8 (s, 2H). IR (KBr, cm^{-1}) 3400, 3200, 1736, 1636, 1618, 1583, 1499, 1455, 1433, 1329, 1249, 1155, 753, and 713. MS (ES) m/e 449, 451.

Elemental Analyses for $C_{28}H_{22}N_2O_4$:

Calculated: C, 74.65; H, 4.92; N, 6.22.
Found: C, 75.47; H, 4.77; N, 6.24.

EXAMPLE 45

Esterification of {9-[(2-Biphenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid to the {9-[(2-Biphenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, methyl ester



A suspension of the {9-[(2-biphenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid (35 mg, 0.08 mM), iodomethane (12 mg, 0.09 mM), and potassium carbonate (13 mg, 0.09 mM) in 2 mL DMF at room temperature for 4.5 hours. The mixture was diluted with ethyl acetate, washed with H_2O, sat. $NaHCO_3$, H_2O, and saturated brine, dried over magnesium sulfate, filtered, and concentrated to afford 36 mg (100%) of the {9-[(2-biphenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, methyl ester as a white solid. ^1H NMR ($CDCl_3$) δ 7.6-7.2 (m, 11H), 7.1 (t, 1H, J=8 Hz), 6.85 (d, 1H, J=8 Hz), 6.6 (d, 1H, J=8 Hz), 6.55 (d, 1H, J=8 Hz), 5.8 (br s, 2H), 5.4 (s, 2H), 4.8 (s, 2H), and 3.75 (s, 3H). IR (KBr, cm^{-1}) 1750 and 1666. MS (ES) m/e 465.

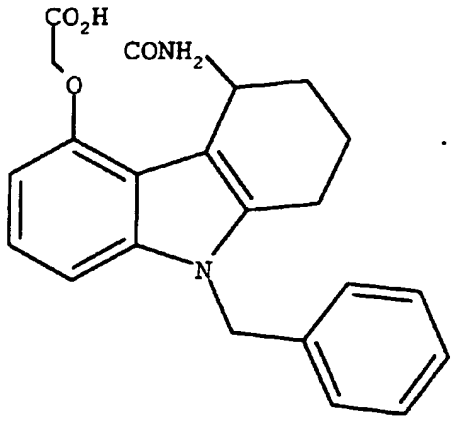
Elemental Analyses for $C_{29}H_{24}N_2O_4$:

Calculated: C, 74.98; H, 5.21; N, 6.03.

Found: C, 75.09; H, 5.57; N, 5.63.

Example 46

Preparation of [9-Benzyl-4-carbamoyl-1,2,3,4-tetrahydrocarbaole-5-yl]oxyacetic acid



A. 9-Benzyl-4-carboxy-5-methoxy-1,2,3,4-tetrahydrocarbazole, Ethyl Ester.

A solution of 1.50 g (4.02 mmol) of 9-Benzyl-4-carboxy-8-chloro-5-methoxy-1,2,3,4-tetrahydrocarbazole, ethyl ester and 0.45 g (4.40 mmol) of Et_3N in 25 mL of EtOH was treated with 0.24 g of 5% Pd-C and the mixture hydrogenated at 60 pounds per square inch for 16 hours. The reaction was filtered and concentrated *in vacuo* to give 1.40 g of a tan solid. ^1H NMR ($CDCl_3$) δ 7.30-7.19 (m, 3H), 7.03-6.95 (m, 3H), 6.80 (d, 1H, J=8.1 Hz), 6.44 (d, 1H, J=7.7 Hz), 5.22 (d, 2H, J=5.9 Hz), 4.22-4.11 (m, 3H), 3.82 (s, 3H), 2.75-2.64 (m, 1H), 2.59-2.48 (m, 1H), 2.11-1.64 (m, 4H), and 1.25 (t, 3H, J=7.0 Hz). IR ($CHCl_3$) 2959, 1725, 1499, 1453, 1260, 1178, 1128 cm-1;

Elemental Analyses for $C_{23}H_{25}NO_3$:

Calculated: 363.1836

Found: 363.1834.

B. 9-Benzyl-4-carbamoyl-5-hydroxy-1,2,3,4-tetrahydrocarbazole.

A 0 °C solution of 1.00 g (2.80 mmol) 9-benzyl-4-carboxy-5-methoxy-1,2,3,4-tetrahydrocarbazole, ethyl ester in 15 mL of CH_2Cl_2 was treated with 22.40 mL (22.40 mmol; 1M in CH_2Cl_2) of BBr_3. The cold bath was removed and the reaction stirred until tlc analysis (10% EtOAc in hexanes) indicated complete consumption of starting material (1.5 hours). The reaction was cooled to 0 °C and was quenched with 5.0 mL of MeOH. The mixture was stirred at ambient temperature for 18 hours and was concentrated *in vacuo*. The black oil was taken up in 200 mL of CH_2Cl_2 and the solution washed with H20 (100 mL) and saturated aqueous $NaHCO_3$ (100mL). Evaporation of the solvent *in vacuo* afforded 700 mg of a black oil. Purification by radial chromatography (10 % EtOAc in hexanes) afforded 400 mg of 9-benzyl-4-carboxy-5-hydroxy-1,2,3,4-tetrahydrocarbazole, ethyl ester which was taken on directly to the next reaction

The phenol was taken up in 40 ml of THF and the solution treated with 10 mL of NH_4OH. The reaction vessel was capped and the mixture stirred vigorously for 13 days. The reaction was poured into H_2O and the mixture extracted with EtOAc (3 x 150 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo* to give 300 mg of a brown foam. Radial chromatography (3% MeOH in CH_2Cl_2) afforded 50 mg of starting phenol and 80 mg (0.03 mmol; 22 %) of 9-benzyl-4-carbamoyl-5-hydroxy-1,2,3,4-tetrahydrocarbazole. ^1H NMR ($CDCl_3$) δ 7.33-7.24 (m, 3H), 7.06-6.97 (m, 3H), 6.81 (d, 1H, J=8.1 Hz), 6.56 (d, 1H, J=7.5 Hz), 5.22 (d, 2H, J=2.2 Hz), 4.20-4.15 (m, 1H), 2.78-2.67 (m, 1H), 2.63-2.51 (m, 1H), 2.35-2.27 (m, 1H), and 2.09-1.91 (m, 3H), no phenol proton detected. IR (CHCl3) 3007, 1667, 1586, 1567, 1496, 1266 cm-1;

Elemental Analyses for $C_{20}H_{21}N_2O_2$:

Calculated: 321.1603.

Found: 321.1607.

C. [9-Benzyl-4-carbamoyl-1,2,3,4-tetrahydrocarbazole-5-yl]oxyacetic acid, Methyl Ester.

A solution of 80 mg (0.25 mmol) of 9-benzyl-4-carbamoyl-5-hydroxy-1,2,3,4-tetrahydrocarbazole in 2.5 mL of DMF was treated with 61 mg (0.30 mmol) of Cs_2CO_3 followed by 26 mg (0.30 mmol) of methyl bromoacetate. The mixture was stirred at room temperature until tlc indicated complete consumption of starting material (2 hours). The reaction was diluted with H_2O (10 mL) and was extracted with EtOAc (3x10 mL). The combined organic layers were washed with H_2O (3 x2 0 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by radial chromatography (SiO_2; 2.5% MeOH in CH_2Cl_2) to afford 50 mg (0.13 mmol; 51%) of [9-benzyl-4-carbamoyl-1,2,3,4-tetrahydrocarbazole-5-yl]oxyacetic acid, methyl ester as an oil. ^1H NMR ($CDCl_3$) δ 7.33-7.21 (m, 3H), 7.05-6.98 (m, 3H), 6.98 (d, 1H, J=7.4 Hz), 6.46 (br s, 1H), 6.37 (d, 1H, J=7.7 Hz), 5.52 (br s, 1H), 5.23 (d, 1H, J=4.9 Hz) 4.79-4.70 (m, 2H), 4.20-4.15 (m, 1H), 3.81 (s, 3H), 2.79-2.69 (m, 1H), 2.63-2.49 (m, 1H), 2.43-2.35 (m, 1H), 2.25-2.09 (m, 1H), and 1.99-1.78 (m, 2H). IR ($CHCl_3$, cm^{-1}) 1759, 1670, 1497, 1453, 1440, and 1132. MS (ES) m/e 393 (M+1).

Elemental Analyses for $C_{23}H_{24}N_2O_4$:

Calculated: C, 70.39; H, 6.16; N, 7.14.

Found: C, 70.29; H, 6.31; N, 7.08.

D. [9-Benzyl-4-carbamoyl-1,2,3,4-tetrahydrocarbazole-5-yl]oxyacetic acid

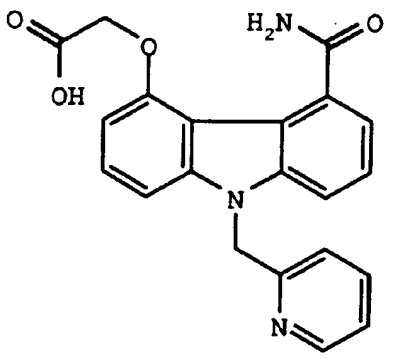
A solution of 30 mg (0.076 mmol) of [9-benzyl-4-carbamoyl-1,2,3,4-tetrahydrocarbazole-5-yl]oxyacetic acid, methyl ester in 1.0 mL of THF and 1.0 mL of MeOH was treated with 0.2 mL of 1 N aqueous LiOH (0.2 mmol). The mixture was stirred for 18 hours. An additional 0.2 mL of 1 N aqueous LiOH (0.2 mmol) was added and stirring continued. After 1 hour, the mixture was concentrated *in vacuo*. The residue was dissolved in 2.0 mL of H_2O and the solution acidified with 0.2 N aqueous HCl. The solid was filtered and dried to afford 25 mg of [9-benzyl-4-carbamoyl-1,2,3,4-tetrahydrocarbazole-5-yl]oxyacetic acid as a white solid. ^{1}H NMR (DMSO-d6) δ 7.36-7.12 (m, 5H), 7.05-6.83 (m, 5H), 6.71 (br s, 1H), 6.35 (d, 1H, J=7.6 Hz), 5.27 (s, 2H), 4.64 (s, 2H), 3.93-3.84 (m, 2H), 2.75-2.64 (m, 1H), 2.16-1.95 (m, 2H), 1.81-1.64 (m, 2H) and 1 proton masked by H_2O peak between 2.58-2.40. IR (KBr, cm^{-1}) 3435, 2936, 1722, 1644, 1586, 1566, 1495, 1451, 1354, 1227, 1134, 730, 716, and 698. MS (ES) m/e 377 (M-1) and 379 (M+1).

Elemental Analyses for $C_{22}H_{22}N_2O_4$:

Calculated:	C, 69.83; H, 5.86; N, 7.40.
Found:	C, 70.11; H, 5.76; N, 7.12.

EXAMPLE 47

Preparation of {9-[(2-Pyridyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid



A. 9-[(2-Pyridyl)methyl]-5-carbomethoxy-1,2-dihydrocarbazol-4(3H)-one

A 0 °C suspension of 5-carbomethoxy-1,2-dihydro-9H-carbazol-4(3H)-one (1.50 g, 6.17 mmol), potassium carbonate (2.60 g, 18.8 mmol), and catalytic amount of sodium iodide (ca. 10 mg), was treated with 2-picolyl chloride hydrochloride (1.10 g, 6.70 mmol). The cold bath was removed and the reaction stirred at ambient temperature 72 hours. The reaction was poured into H_2O (100 mL) and the mixture extracted four times with ethyl acetate. The combined organic layers were washed four times with H_2O, once with saturated brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by flash chromatography on silica gel (elution with 70% then 80% then 85% EtOAc in hexanes) to afford 1.70 g (82%) of the 9-[(2-pyridyl)methyl]-5-carbomethoxy-1,2-dihydrocarbazol-4(3H)-one as an oil which solidified on standing. ^1H NMR ($CDCl_3$) δ 8.52 (br s, 1H), 7.54-7.47 (m, 1H), 7.34-7.26 (m, 2H), 7.18-7.11 (m, 2H), 6.67 (d, J=7.8 Hz, 1H) 5.34 (s, 2H), 3.99 (s, 3H), 2.87 (t, 2H, J=6.0 Hz), 2.50 (t, 2H, J=6.3 Hz), and 2.20-2.13 (m , 2H). IR ($CHCl_3$,

cm^{-1}) 3010, 2953, 1725, 1654, 1463, 1446, 1288 and 1121. MS (ES) m/e 335 (M+1).

Elemental Analyses for $C_{20}H_{16}N_2O_3$:

Calculated: C, 71.84; H, 5.43; N, 8.38.

Found: C, 71.70; H, 5.49; N, 8.37.

B. 9-[(2-Pyridyl)methyl]-4-hydroxy-5-carbomethoxy carbazole

A solution of the 9-[(2-pyridyl)methyl]-5-carbomethoxy-1,2-dihydrocarbazol-4(3H)-one (500 mg, 1.50 mmol) in 2 mL of dioxane was treated with sodium hydride (140 mg; 3.50 mmol; 60% dispersion in mineral oil) and the mixture stirred for 15 minutes. Methyl benzenesulfinate (0.32 mL; 2.45 mmol) was added dropwise and the reaction stirred at room temperature. After 0.5 hours, gas evolution began and the reaction turned dark brown. The mixture was stirred until tlc indicated complete consumption of starting material (1 hour) at which time glacial acetic acid (0.20 mL; 3.50 mmol) was added. An additional 2 mL of dioxane was added to assist stirring and the mixture was heated to mild reflux for 1 hour. The reaction was cooled and diluted with EtOAc (50 mL). The organic layer was separated, washed once with saturated aqueous. $NaHCO_3$ and once with saturated brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by radial chromatography on silica gel (elution with 20% ethyl acetate in hexanes) to afford 470.0 mg (94%) of the 9-[(2-pyridyl)methyl]-4-hydroxy-5-carbomethyoxy carbazole as a solid. ^1H NMR ($CDCl_3$) δ 10.37 (s, 1H), 8.61 (d, 1H, J=3.7 Hz), 8.01 (d, 1H, J=7.8 Hz), 7.63 (d, 1H, J=8.3 Hz), 7.47-7.39 (m, 3H), 7.19-7.14 (m, 1H), 6.94 (d, 1H, J=8.3 Hz), 6.84 (d, 1H, J=8.3 Hz), 6.59 (d, 1H, J=7.8 Hz), 5.66 (s, 2H), and 4.10 (s, 3H). IR ($CHCl_3$, cm^{-1}) 3200 (br), 1686,

1597, 1442, 1428, 1332, 1286, and 1268. MS (ES) m/e 333 (M+1).

Elemental Analyses for $C_{20}H_{16}N_2O_3$:

Calculated: C, 72.28; H, 4.85; N, 8.43.

Found: C, 72.44; H, 4.79; N, 8.44.

c. 9-[(2-Pyridyl)methyl]-4-hydroxy-5-carbamoyl carbazole

A solution of the 9-[(2-pyridyl)methyl]-4-hydroxy-5-carbomethoxy carbazole (480 mg, 1.43 mmol) in 10 mL THF and 40 mL concentrated aqueous ammonium hydroxide was treated with a stream of NH_3 gas to ensure saturation. The reaction vessel was capped and the mixture heated to 35 °C with stirring until tlc indicated complete consumption of starting material (20 hours). The THF was evaporated and the aqueous layer saturated with solid sodium chloride. The mixture was extracted three times with THF. The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated. The foam was taken up in hot ethyl acetate and passed over a shoroom temperaturecolumn of silica gel using ethyl acetate as the eluent to afford 247 mg (54%) of the 9-[(2-pyridyl)methyl]-4-hydroxy-5-carbamoyl carbazole as a white solid. ^{1}H NMR (DMSO-d6) δ 10.46 (s, 1H), 8.81 (br s, 1H), 8.46 (d, 1H, J=5.8 Hz), 8.36 (br s, 1H), 7.8 (dd, 1H, J=2.9 and 6.4 Hz), 7.67-7.59 (m, 1H), 7.47-7.41 (m, 2H), 7.30-7.20 (m, 2H), 7.05 (d, 1H, J=7.9 Hz), 6.87 (d, 1H, J=8.3 Hz), 6.57 (d, 1H, J=7.8 Hz), and 5.73 (s, 2H). IR (KBr, cm^{-1}) 3404, 3051, 1652, 1618, 1595, 1582, 1567, 1559, 1450, 1436, 1334, 1266, 1226, 776, 763 and 647. MS (ES) m/e 318 (M+1).

Elemental Analyses for $C_{19}H_{15}N_3O_2$:

Calculated: C, 71.91; H, 4.76; N, 13.24.

Found: C, 72.11; H, 4.70; N, 12.95.

D. {9-[(2-Pyridyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, methyl ester

A mixture of the 9-[(2-pyridyl)methyl]-4-hydroxy-5-carbamoyl carbazole (216 mg, 0.68 mmol) and Cs_2CO_3 (550 mg; 1.69 mmol) in 5 mL DMF was treated with methyl bromoacetate (0.08 mL; 0.85 mmol). The reaction was stirred until tlc analysis indicated complete consumption of starting material (2 hours). The mixture was concentrated and the residue taken up in H_2O (50 mL). The aqueous layer was saturated with solid NaCl and was extracted five times with THF. The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated. The solid was triturated with EtOAc to afford 205 mg (77%) of the {9-[(2-pyridyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, methyl ester as an off white solid. ^1H NMR (DMSO-d6) δ 8.47 (d, 1H, J=4.9 Hz), 7.66-7.57 (m, 2H), 7.48 (br s, 1H), 7.38-7.27 (m, 2H), 7.24-7.19 (m, 2H), 7.19 (br s, 1H), 7.04 (d, 1H, J=7.3 Hz), 6.87 (d, 1H, J=7.8 Hz), 6.56 (d, 1H, J=7.8 Hz), 5.71 (s, 2H), 4.89 (s, 2H), and 3.69 (s, 3H). IR ($CHCl_3$, cm^{-1}) 3380, 3140, 1737, 1675, 1500, 1457, 1354, 1340, 1242, 1158, 772, and 715. MS (ES) m/e 390 (M+1).

Elemental Analyses for $C_{22}H_{19}N_3O_4$:

Calculated:	C, 67.86; H, 4.92; N, 10.79.
Found:	C, 67.75; H, 5.08; N, 10.66.

E. {9-[(2-Pyridyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, hydrochloride

A slurry of the {9-[(2-pyridyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, methyl ester (75.0 mg, 0.19 mmol) in 1.3 mL of THF and 0.4 mL of MeOH was treated with 0.4 mL of 1 N aqueous LiOH (0.4 mmol) and the mixture stirred at room temperature for 16 hours. The reaction was concentrated and the residue purified by

reverse phase chromatography (Vydac C18 column using a 5% to 40% gradient of 0.01% HCl in acetonitrile in 0.01% HCl in H_2O. The fractions containing product were lyopholized to afford 75 mg (96%) of {9-[(2-pyridyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid hydrochloride as a white powder. ^1H NMR (DMSO-d6) δ ^1H NMR (DMSO-d6) δ 8.50-8.46 (m, 1H), 7.71 (br s, 1H), 7.62-7.67 (m, 1H), 7.58 (d, 1H, J=8.3 Hz), 7.38 (br s, 1H), 7.42-7.29 (m, 3H), 7.26-7.19 (m, 2H), 7.06 (d, 1H, J=7.3 Hz), 6.87 (d, 1H, J=7.8 Hz), 6.58 (d, 1H, J=8.3 Hz) 5.73 (s, 2H) and 4.80 (s, 2H), no acid proton detected. IR (KBr, cm^{-1}) 3381, 1716, 1637, 1593, 1580, 1499, 1454, 1430, 1330, 1287, 1157, 1093, 776 and 720. MS (ES) m/e376 (M+1).

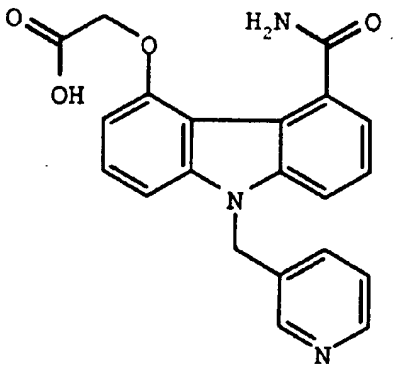
Elemental Analyses for $C_{21}H_{17}N_3O_4.HCl$:

Calculated: C, 61.24; H, 4.41; N, 10.20.

Found C, 61.11; H, 4.25; N, 10.23.

EXAMPLE 48

Preparation of {9-[(3-Pyridyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid



A. 9-[(3-Pyridyl)methyl]-5-carbomethoxy-1,2-dihydrocarbazol-4(3H)-one.

A suspension of 5-carbomethoxy-1,2-dihydro-9H-carbazol-4(3H)-one (500 mg, 2.06 mmol), potassium carbonate (860 mg,

18.8 mmol), and catalytic amount of sodium iodide (ca. 10 mg), was treated with 3-picolyl chloride hydrochloride (500 mg, 3.05 mmol). The reaction was stirred at ambient temperature 19.5 hours. The mixture was poured into H_2O (100 mL) and the mixture extracted four times with ethyl acetate. The combined organic layers were washed four times with H_2O, once with saturated brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by flash chromatography on silica gel (elution with 5% MeOH in EtOAc) to afford 550 mg (80%) of the 9-[(3-pyridyl)methyl]-5-carbomethoxy-1,2-dihydrocarbazol-4(3H)-one as a white solid. ^{1}H NMR ($CDCl_3$) δ 8.48 (d, 1H, J=2.9 Hz), 8.43 (br s, 1H), 7.31 (d, 1H, J=7.3 Hz), 7.25-7.09 (m, 5H), 5.29 (s, 2H), 3.97 (s, 3H), 2.80 (t, 2H, J=6.1 Hz), 2.49 (t, 2H, J=6.4 Hz), and 2.20-2.12 (m , 2H). IR ($CHCl_3$, cm^{-1}) 1726, 1656, 1464, 1444, 1434, 1289 and 1119. MS (ES) m/e 335 (M+1).

Elemental Analyses for $C_{20}H_{18}N_2O_3$:

Calculated: C, 71.84; H, 5.43; N, 8.38.

Found: C, 70.97; H, 5.89; N, 8.53.

B. 9-[(3-Pyridyl)methyl]-4-hydroxy-5-carbomethoxy carbazole.

A solution of the 9-[(3-pyridyl)methyl]-5-carbomethoxy-1,2-dihydrocarbazol-4(3H)-one (456 mg, 1.31 mmol) in 3 mL of dioxane was treated with sodium hydride (128 mg; 3.20 mmol; 60% dispersion in mineral oil) and the mixture stirred for 15 minutes. Methyl benzenesulfinate (0.32 mL; 2.45 mmol) was added dropwise and the reaction heated to 70 °C until tlc analysis indicated complete consumption of starting material (2 hours). The reaction was cooled and diluted with EtOAc (50 mL). The organic layer was separated, washed once with saturated aqueous. $NaHCO_3$ and once with saturated

brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by radial chromatography on silica gel (elution with 20% then 30 % then 50% then 75% ethyl acetate in hexanes) to afford 400 mg (92%) of the 9-[(3-pyridyl)methyl]-4-hydroxy-5-carbomethyoxy carbazole as a yellow solid. ^{1}H NMR (DMSO-d6) δ 10.20 (s, 1H), 8.46 (d, 1H, J=2.0 Hz), 8.39 (d, 1H, J=4.9 Hz), 7.73 (d, 1H, J=8.3 Hz), 7.43-7.37 (m, 2H), 7.28-7.21 (m, 2H), 7.15-7.08 (m, 2H), 6.56 (d, 1H, J=7.8 Hz), 5.67 (s, 2H), and 3.80 (s, 3H). IR (KBr, cm^{-1}) 1722, 1585, 1459, 1431, 1331, 1321, 1292, 1278, 1136, 781 and 763. MS (ES) m/e 333 (M+1).

Elemental Analyses for $C_{20}H_{16}N_2O_3$:

Calculated: C, 72.28; H, 4.85; N, 8.43.

Found: C, 72.37; H, 4.67; N, 8.71.

C. 9-[(3-Pyridyl)methyl]-4-hydroxy-5-carbamoyl carbazole.

A solution of the 9-[(3-pyridyl)methyl]-4-hydroxy-5-carbomethoxy carbazole (362 mg, 1.09 mmol) in 15 mL THF and 60 mL concentrated aqueous ammonium hydroxide was treated with a stream of NH_3 gas to ensure saturation. The reaction vessel was capped and the mixture heated to 35 °C with stirring until tlc indicated complete consumption of starting material (48 hours). The mixture was neutralized to pH 8 with 5 N aqueous HCl, saturated with solid sodium chloride, and extracted twice with THF. The combined organic layers were concentrated. The resulting foam was taken up in a minimal amount of THF and loaded onto a silica gel column which had been pre equilibrated with EtOAc. Elution with EtOAc afforded 255 mg (74%) of the 9-[(3-pyridyl)methyl]-4-hydroxy-5-carbamoyl carbazole as a yellow solid. ^{1}H NMR (DMSO-d6) δ 10.46 (s, 1H), 8.79 (br s, 1H), 8.43 (d, 1H, J=1.5 Hz), 8.39 (dd, 1H, J=1.4 and 4.9 Hz), 8.35 (br s, 1H), 7.84 (d, 1H, J=7.8 Hz), 7.48-7.22 (m, 6H),

7.13 (d, 1H, J=8.3 Hz), 6.58 (d, 1H, J=7.8 Hz), and 5.73 (s, 2H). IR (KBr, cm^{-1}) 3436, 3198 (br), 1629, 1619, 1599, 1580, 1564, 1547, 1444, 1433, 1329, 1263, and 776. MS (ES) m/e 318 (M+1).

Elemental Analyses for $C_{19}H_{15}N_3O_2$:

Calculated: C, 71.91; H, 4.76; N, 13.24.

Found: C, 72.10; H, 4.66; N, 13.19.

D. {9-[(3-Pyridyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, methyl ester.

A mixture of the 9-[(3-pyridyl)methyl]-4-hydroxy-5-carbamoyl carbazole (225 mg, 0.71 mmol) and Cs_2CO_3 (580 mg; 1.78 mmol) in 5 mL DMF was treated with methyl bromoacetate (0.09 mL; 0.95 mmol). The reaction was stirred until tlc analysis indicated complete consumption of starting material (2 hours). The mixture was concentrated and the residue taken up in H_2O (50 mL). The aqueous layer was saturated with solid NaCl and was extracted five times with THF. The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated. The solid was triturated with THF then EtOAc to afford 85 mg of the {9-[(2-pyridyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, methyl ester as an off white solid. The mother liquors from the triturations were chromatographed over silica gel using radial chromatography (0.5% then 1% then 2% MeOH in $CHCl_3$) to afford an additional 80 mg of product (165 mg total; 60%). ^1H NMR ($CDCl_3$) δ 8.53 (br, 2H), 7.42-7.39 (m, 4H), 7.20 (d, 1H, J=7.8 Hz), 7.13 (br s, 1H), 6.98 (d, 1H, J=8.3 Hz), 6.56 (d, 1H, J=7.9 Hz), 6.17 (br s, 1H), 5.91 (br s, 1H), 5.49 (s, 2H), 4.88 (s, 2H), and 3.79 (s, 3H). IR (KBr, cm^{-1}) 3367, 3161, 1760, 1733, 1673, 1577, 1501, 1458, 1433, 1418, 1328, 1216, 1202, 1180, 1157, 771, and 714. MS (ES) m/e 373 (M^+-NH_2) and 390 (M+1).

E. {9-[(3-Pyridyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, hydrochloride

A slurry of the {9-[(3-pyridyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, methyl ester (85.0 mg, 0.22 mmol) in 1.5 mL of THF and 0.48 mL of MeOH was treated with 0.48 mL of 1 N aqueous LiOH (0.48 mmol) and the mixture stirred at room temperature for 16 hours. The reaction was concentrated and the residue purified by reverse phase chromatography (Vydac C18 column using a 5% to 40%-gradient of 0.01% HCl in acetonitrile in 0.01% HCl in H_2O. The fractions containing product were lyopholized to afford 63 mg (70%) of {9-[(3-pyridyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid hydrochloride as a white powder. ^{1}H NMR (DMSO-d6) δ 8.62-8.57 (m, 2H), 7.77-7.67 (m, 3H), 7.62-7.54 (m, 1H), 7.43-7.28 (m, 4H), 7.09 (d, 1H, J=6.3 Hz), 6.61 (d, 1H, J=7.8 Hz), 5.81 (s, 2H) and 4.80 (s, 2H), no acid proton detected. IR (KBr, cm^{-1}) 3424, 3324, 1728, 1671, 1655, 1616, 1595, 1579, 1500, 1456, 1421, 1328, 1203, 1156, and 772. MS (ES) m/e 374 (M-1), 376 (M+1).

Elemental Analyses for $C_{22}H_{17}N_3O_4.HCl$:

Calculated:	C, 61.24; H, 4.41; N, 10.20.
Found:	C, 61.28; H, 4.25; N, 10.28.

Example 49

Preparation of [9-benzyl-4-carbamoyl-8-methyl-1,2,3,4-tetrahydrocarbazol-5-yl]oxyacetic acid

A. Preparation of ethyl 5-methoxy-8-methyl-1,2,3,4-tetrahydrocarbazole-4-carboxylate

A solution of 1.87 g (13.65 mmol) of 2-methyl-5-methoxyaniline and 3.40 g (13.65 mmol) of 2-carboethoxy-6-

bromocyclohexanone (Sheehan and Mumaw, JACS, 72, 2127 (1950)) in 10 ml of anhydrous dimethylformamide was heated at 55°C for 13 hours. The reaction mixture was cooled, poured into brine and extracted twice with diethyl ether. The extracts were washed twice with water and then with brine, dried over magnesium sulfate and concentrated. The residue was chromatographed on silica gel using a 10:1 hexane/ethyl acetate mixture to afford 2.88 g (69 %) of a mixture of diastereomers of N-alkylated material. This mixture was refluxed in 90 ml of benzene with 4.69 g (34.4 mmol) of zinc chloride for 10 hours. The solvent was evaporated and the residue was partitioned between 80 ml of 1 N HCl and 80 ml of ethyl acetate and then extracted once more with ethyl acetate. The organic layers were washed with water and then brine, dried over magnesium sulfate and concentrated to afford 2.60 g (95%) of the subtitled compound. m.p. 119-122°C

Elemental Analyses

Calculated:	C 71.06; H 7.37; N 4.87
Found:	C 71.35; H 7.25; N 4.92

B. Preparation of ethyl 9-benzyl-5-methoxy-8-methyl-1,2,3,4-tetrahydrocarbazole-4-carboxylate

A solution of 1.58 g of ethyl 5-methoxy-8-methyl-1,2,3,4-tetrahydrocarbazole-4-carboxylate in 5 ml of dimethylformamide was added to 0.24 g of sodium hydride (60% in mineral oil) in 5 ml of dimethylformamide and stirred for 30 minutes at room temperature. Potassium iodide (90 mg) and 0.75 ml of benzyl bromide were then added and the reaction was stirred overnight. The reaction mixture was poured into 75 ml of saturated ammonium chloride solution and then extracted twice with ether. The extracts were washed with water and then with brine, dried over magnesium

sulfate and concentrated. The residue was chromatographed on silica gel using hexane/ethyl acetate mixtures to afford 1.09 g (53%) of the subtitle compound. ESIMS *m/e* 378 (M^++1) NMR (300 MHz, $CDCl_3$): δ 7.28-7.19 (m, 3H); 6.84 (d, J=7.4, 2H); 6.67 (d, J=7.8, 1H); 6.33 (d, J=7.9, 1H); 5.55 and 5.39 (ABq, J=7.8, 2H); 4.17 (q+m, J=6.9, 3H); 3.80 (s, 3H); 2.64 (dt, J=16.1, 5.3, 1H); 2.48 (dt, J=16.6, 6.9,1H); 2.41 (s, 3H); 2.05 (m, 2H); 1.95 (m, 1H); 1.83 (m, 1H); 1.25 (t, J=7.3, 3H).

C. Preparation of 9-benzyl-5-methoxy-8-methyl-1,2,3,4-tetrahydrocarbazole-4-carboxamide

A slurry of 0.38 g of ammonium chloride in 15 ml of dry toluene was cooled in an ice bath and treated with 3.5 ml of a 2.0 M solution of trimethylaluminum in toluene. This mixture was stirred for 1 hour at room temperature, whereupon 0.762 g (2.02 mmol) of ethyl 9-benzyl-5-methoxy-8-methyl-1,2,3,4-tetrahydrocarbazole-4-carboxylate in 10 ml of toluene and 1 ml of dichloromethane was added. The mixture was heated to 50°C overnight, cooled and quenched with 20 ml of aqueous 5% HCl solution. Ethyl acetate extracts (3x 100 ml) were washed with water and then with brine, dried over magnesium sulfate and concentrated to afford 0.693 g (98%) of the subtitle compound. ESIMS *m/e* 349 (M^++1) NMR (300 MHz, $CDCl_3$): δ 7.25 (m, 3H); 6.83 (d, J=7.2, 2H); 6.74 (d, J=7.8, 1H); 6.40 (d, J=7.8, 1H); 5.93 (br, 1H); 5.54 and 5.45 (ABq, J=17.7, 2H); 5.42 (br, 1H); 4.14 (br, 1H); 3.87 (s, 3H); 2.65 (dt, J=16.4, 4.1, 1H); 2.55-2.36 (m,2H); 2.45 (s, 3H); 1.97-1.86 (m, 3H).

D. Preparation of [9-benzyl-4-carbamoyl-8-methyl-1,2,3,4-tetrahydrocarbazol-5-yl]oxyacetic acid methyl ester

A solution of 0.661 g of 9-benzyl-5-methoxy-8-methyl-1,2,3,4-tetrahydrocarbazole-4-carboxamide in 50 ml of dry dichloromethane was cooled to -40°C and treated dropwise with 1.8 ml of neat boron tribromide. The reaction was stirred for 2 hours at room temperature and quenched by pouring into ice and adding 1 N HCl solution. This mixture was extracted twice with dichloromethane and the organic layers were dried over magnesium sulfate and concentrated to afford 0.625 g of the demethylated compound.

A solution of 0.55 g of this intermediate in 10 ml of dimethylformamide was cooled in an ice bath and treated with 1.61 g of cesium carbonate and 0.16 ml of methyl bromoacetate. After stirring for 1 hour at room temperature, the reaction mixture was poured into water and extracted twice with ethyl acetate. The extracts were washed with water and then with brine, dried over magnesium sulfate and concentrated. The residue was chromatographed on silica gel using methanol/ 0-2% in dichloromethane to afford 0.46 g (69%) of the subtitle compound. m.p. 209°C

Elemental Analyses

Calculated:	C 70.92; H 6.45; N 6.89
Found:	C 70.85; H 6.19; N 6.98

E. Preparation of [9-benzyl-4-carbamoyl-8-methyl-1,2,3,4-tetrahydrocarbazol-5-yl]oxyacetic acid]

A slurry of 64 mg (0.157 mmol) of [9-benzyl-4-carbamoyl-8-methyl-1,2,3,4-tetrahydrocarbazol-5-yl]oxyacetic acid methyl ester in 2 ml of tetrahydrofuran and 7 ml of methanol was treated with 0.5 ml of an aqueous 2 N sodium hydroxide solution and stirred overnight at room temperature. The solvent was evaporated and the residue was

partitioned between ethyl acetate and 1 N HCl solution. After another extraction with ethyl acetate, the extracts were washed with brine, dried over magnesium sulfate and concentrated to afford a quantitative yield (62 mg) of the title compound. ESIMS *m/e* 393 (M^++1), 391 (M^+-1). NMR (300 MHz, d^6-DMSO): δ 12.98 (br, 1H); 7.30-7.18 (m, 3H); 6.82 (d+br, J=7.0, 3H); 6.73 (br, 1H); 6.59 (d, J=7.9,1H); 6.26 (d, J=7.9, 1H); 5.53 and 5.45 (ABq, J=18.1, 2H); 4.62 (s, 2H); 3.96 (br, 1H); 2.63 (m, 1H); 2.43 (m, 1H); 2.34 (s, 3H); 2.04 (m, 2H); 1.78 (m, 2H).

Elemental Analyses

Calculated:	C 70.39; H 6.16; N 7.14
Found:	C 70.41; H 6.44; N 6.88

Example 50

Preparation of [9-benzyl-5-carbamoyl-1-methylcarbazol-4-yl]oxyacetic acid

A. Preparation of 5-carbamoyl-4-methoxy-1-methylcarbazole

A solution of 0.805 g of 9-benzyl-5-methoxy-8-methyl-1,2,3,4-tetrahydrocarbazole-4-carboxamide in 24 ml of carbitol was treated with 1.1 g of 5% palladium on carbon and was refluxed for 6 hours open to the air. After cooling, the solution was filtered thourough a pad of celite and the pad was washed with ethyl acetate. The filtrates were diluted with ether and washed four times with water and dried over magnesium sulfate and concentrated. The residue was chromatographed on silica gel using methanol/0-4% in dichloromethane to afford 0.166 g (28%) of debenzylated carbazole. ESIMS *m/e* 255 (M^++1), 253 (M^+-1) NMR (300 MHz, $CDCl_3$): δ 8.13 (br, 1H); 7.51 (d, J=8.1, 1H); 7.40 (t,

J=7.6, 1H); 7.32 (d, J=7.2, 1H); 7.18 (d, J=7.8, 1H); 6.60 (d, J=8.0, 1H); 5.68 (br, 2H); 3.99 (s, 3H); 2.50 (s 3H).

B. Preparation of 9-benzyl-5-carbamoyl-4-methoxy-1-methylcarbazole

A solution of 0.148 g of 5-carbamoyl-4-methoxy-1-methylcarbazole in 1.1 ml of dimethylformamide was added to 0.026 g of sodium hydride (60% in mineral oil) in 0.4 ml of dimethylformamide and stirred for 60 minutes at room temperature. Benzyl bromide (0.076 ml) was then added and the reaction was stirred overnight. The reaction mixture was poured into 20 ml of saturated ammonium chloride solution and then extracted twice with ethyl acetate. The extracts were washed with water and then with brine, dried over magnesium sulfate and concentrated. The residue was rinsed with hexane and dissolved in dichloromethane, filtered and concentrated to afford 0.21 g of the subtitle compound. FDMS *m/e* 344 (M^+)

Elemental Analyses

Calculated:	C 76.72;	H 5.85; N 8.13
Found:	C 75.20;	H 6.19; N 7.54

C. Preparation of [9-benzyl-5-carbamoyl-1-methylcarbazol-4-yl]oxyacetic acid methyl ester]

A solution of 0.23 g of 9-benzyl-5-carbamoyl-4-methoxy-1-methylcarbazole in 4 ml of dimethylformamide was added to a 1 ml solution of sodium ethane thiolate (prepared from 0.116 g of sodium hydride 60% dispersion and 0.22 ml of ethanethiol under nitrogen) and heated at 110°C for 15 hours. The reaction mixture was cooled, poured into 20 ml of 1 N HCl and extracted twice with ethyl acetate. The extracts were washed twice with water and then with brine,

dried over magnesium sulfate and concentrated. The residue was chromatographed on silica gel using methanol/0-1% in dichloromethane to afford 0.146 g (66%) of the demethylated intermediate. A solution of 0.146 g of this intermediate in 1.5 ml of dimethylformamide was added to 0.021 g of sodium hydride (60% in mineral oil) in 0.5 ml of dimethylformamide. After stirring for 10 minutes at room temperature, 0.054 ml of methyl bromoacetate was added. After stirring for 5 hours at room temperature, the reaction mixture was poured into water and extracted twice with ethyl acetate. The extracts were washed with water and then with brine, dried over magnesium sulfate and concentrated. The residue was chromatographed on silica gel using methanol/ 0-2% in dichloromethane to afford 0.10 g (56%) of the subtitle compound. mp. 228-230°C ESIMS *m/e* 403 (M^++1)

Elemental Analyses

Calculated:	C 71.63; H 5.51; N 6.96
Found:	C 71.34; H 5.60; N 6.70

D. Preparation of [9-benzyl-5-carbamoyl-1-methylcarbazol-4-yl]oxyacetic acid

A slurry of 32 mg (0.0795 mmol) of [9-benzyl-5-carbamoyl-1-methylcarbazol-4-yl]oxyacetic acid methyl ester in 1 ml of tetrahydrofuran and 3.5 ml of methanol was treated with 0.3 ml of an aqueous 2 N sodium hydroxide solution and stirred overnight at room temperature. The solvent was evaporated and the residue was partitioned between 1:1 ethyl acetate/tetrahydrofuran and 0.2 N HCl solution. After another extraction with 1:1 ethyl acetate/tetrahydrofuran, the extracts were washed with brine, dried over magnesium sulfate and concentrated to afford (27 mg) of the title compound. mp. 253-254°C. ESIMS *m/e* 389 (M^++1), 387 (M^+-1) NMR (300 MHz, d^6-DMSO): δ

12.83 (br, 1H); 7.75 (br, 1H); 7.53 (d, J=8.2, 1H); 7.41-7.34 (m, 2H); 7.28-7.17 (m, 3H); 7.07 (m, 2H); 6.90 (d, J=7.2, 2H); 6.49 (d, J=8.1, 1H); 5.89 (s, 2H); 4.79 (s, 2H); 2.52 (s, 3H).

Example 51

Preparation of [9-benzyl-4-carbamoyl-8-fluoro-1,2,3,4-tetrahydrocarbazol-5-yl]oxyacetic acid

A. Preparation of (2-chloro-4-fluorophenyl)- ethyl carbonate

A solution of 19.16 g of 2-chloro-4-fluorophenol in 65.4 ml of 2 N aqueous sodium hydroxide solution was cooled in an ice bath and treated dropwise with 16.3 ml of ethyl chloroformate. After stirring at room temperature overnight, the two-phase reaction mixture was diluted with 100 ml of water and extracted with 300 ml of a 1:1 pentane/ether mixture. The extract was washed three times with 0.02 N sodium hydroxide solution, water and then brine. After drying and evaporation, 27.63 g (97%) of the subtitle compound were obtained. NMR (300 MHz, $CDCl_3$): δ 7.23-7.18 (m, 2H); 7.00 (dt, J=8.4, 2.7, 1H); 4.35 (q, J=7.1, 2H); 1.40 (t, J=7.1, 3H).

B. Preparation of (2-chloro-4-fluoro-5-nitrophenyl)- ethyl carbonate

A solution of 27.63 g of (2-chloro-4-fluorophenyl)-ethyl carbonate in 60 ml of dichloromethane was cooled in an ice bath and treated dropwise with 31.86 g of a 1:2 mixture of fuming nitric acid (90%) and concentrated sulfuric acid. The reaction was stirred for 2 hours at room temperature and then cooled with ice and treated with another 4.5 g of the same nitrating mixture. The reaction was stirred overnight

at room temperature, poured into 200 ml of ice and water, and extracted twice with dichloromethane. The extracts were washed with water and then with brine, dried over magnesium sulfate and concentrated to afford 33.01 g (99%) of the subtitle compound. mp. 50-51 C

Elemental Analyses

Calculated:	C 41.01; H 2.68; N 5.31; Cl 13.45
Found:	C 41.03; H 2.59; N 5.38; Cl 13.71

C. Preparation of 2-chloro-4-fluoro-5-nitroanisole

A solution of 15.0 g of (2-chloro-4-fluoro-5-nitrophenyl)- ethyl carbonate in 100 ml of dimethyl formamide was treated with 18.6 g of cesium carbonate, 7.1 ml of iodomethane and 7 ml of methanol and stirred overnight at room temperature. The reaction mixture was poured into water and extracted twice with ether. The extracts were washed twice with water and then with brine, dried over magnesium sulfate and concentrated to afford 11.4g of the subtitle compound. mp. 69-70°C Ex. 57, C.

Elemental Analyses

Calculated:	C 40.90; H 2.45; N 6.81; Cl 17.25
Found:	C 41.20; H 2.48; N 6.70; Cl 17.44

D. Preparation of 2-fluoro-5-methoxyaniline

A solution of 5.63 g of 2-chloro-4-fluoro-5-nitroanisole in 90 ml of ethanol and 5 ml of triethylamine was hydrogenated at room temperature under 60 pounds per square inch with 1.0 g of 5% palladium on carbon for four hours. The catalyst was filtered off and the solvent was evaporated. The residue was slurried in chloroform and filtered thourough a plug of silica gel and then evaporated. This residue was chromatographed on silica gel using hexane/

chloroform mixtures to afford 2.77 g (72%) of the subtitle compound. mp. 253-254°C. NMR (300 MHz, $CDCl_3$): δ 6.88 (dd, J=10.6, 8.9, 1H); 6.32 (dd, J=7.4, 3.0, 1H); 6.20 (dt, J=8.9, 3.2,1H); 3.73 (s, 3H); 3.72 (br, 2H).

E. Preparation of N-benzyl-2-fluoro-5-methoxyaniline

This procedure was patterned after that of Tietze and Grote, Chem Ber. 126(12), 2733 (1993). A solution of 2.73 g of 2-fluoro-5-methoxyaniline and 2.67 g of benzaldehyde in 48 ml of methanol was treated with 3.43 g of zinc chloride and then cooled in an ice bath. Sodium cyanoborohydride (1.58 g) was added in small poroom temperature ions over 30 minutes and the reaction was stirred for five hours at room temperature. After evaporation of the solvent, the residue was slurried in 40 ml of 1 N sodium hydroxide solution and then extracted twice with ether. The extracts were washed with water and then with brine, dried over magnesium sulfate and concentrated. The residue was recrystallized from hexane to afford 2.61 g and the mother liquors were chromatographed on silica gel using 20:1 hexane/ether to afford another 1.4 g of the subtitle compound (90%). mp. 56-58°C

Elemental Analyses

Calculated: C 72.71; H 6.10; N 6.06

Found: C 72.51; H 6.06; N 5.99

F. Preparation of ethyl 9-benzyl-5-methoxy-8-fluoro-1,2,3,4-tetrahydrocarbazole-4-carboxylate

A solution of 0.62 g of N-benzyl-2-fluoro-5-methoxyaniline in 20 ml of dry tetrahydrofuran was cooled in an ice bath and treated with 11.3 ml of 0.5 M potassium bis(trimethylsilyl)amide in toluene. After stirring for 30

minutes, 0.74 g of 2-carboethoxy-6-bromocyclohexanone (Sheehan and Mumaw, JACS, 72, 2127 (1950)) in 4 ml of tetrahydrofuran was added and the reaction was allowed to warm slowly to room temperature over two hours. The reaction was quenched with saturated ammonium chloride solution and extracted twice with ether. The extracts were washed with water and then with brine, dried over magnesium sulfate and concentrated. This residue was chromatographed on silica gel using hexane/ ether mixtures to afford 0.796 g (74%) of N-alkylated intermediate diastereomers. This mixture was refluxed in 20 ml of benzene with 0.99 g of zinc chloride overnight. The solvent was evaporated and the residue was partitioned between 25 ml of 1 N HCl and 25 ml of ethyl acetate and then extracted once more with ethyl acetate. The organic layers were washed with water and then brine, dried over magnesium sulfate and concentrated to afford 0.734 g (96%) of the subtitled compound. ESIMS *m/e* 382 (M^++1)

Elemental Analyses

Calculated:	C 72.42;	H 6.34; N 3.67
Found:	C 72.20;	H 6.26; N 3.70

G. Preparation of 9-benzyl-5-methoxy-8-fluoro-1,2,3,4-tetrahydrocarbazole-4-carboxamide

Ethyl 9-benzyl-5-methoxy-8-fluoro-1,2,3,4-tetrahydrocarbazole-4-carboxylate (0.722 g) was treated similarly as described in Example 49, Part C and chromatographed on silica gel using 1% methanol in dichloromethane to afford 0.482 g (72%) of the subtitle compound. ESIMS *m/e* 353 (M^++1)

Elemental Analyses

Calculated:	C 71.57;	H 6.01; N 7.95
Found:	C 71.42;	H 5.83; N 7.75

H. Preparation of [9-benzyl-4-carbamoyl-8-fluoro-1,2,3,4-tetrahydrocarbazol-5-yl]oxyacetic acid methyl ester

9-Benzyl-5-methoxy-8-fluoro-1,2,3,4-tetrahydrocarbazole-4-carboxamide (0.170 g) was converted similarly as described in Example 49, Part D and chromatographed on silica gel using methanol/ 0-1% in dichloromethane to afford 85 mg (50%) of the subtitle compound. mp. 183-185°C

Elemental Analyses

Calculated:	C 67.31; H 5.65; N 6.82
Found:	C 67.58; H 5.48; N 6.95

I. Preparation of [9-benzyl-4-carbamoyl-8-fluoro-1,2,3,4-tetrahydrocarbazol-5-yl]oxyacetic acid

[9-Benzyl-4-carbamoyl-8-fluoro-1,2,3,4-tetrahydrocarbazol-5-yl]oxyacetic acid methyl ester (71 mg) was hydrolyzed similarly as described in Example 50, Part D to afford 65 mg of the title compound. ESIMS *m/e* 397 (M^++1), 395 (M^+-1) NMR (300 MHz, d^6-DMSO): δ 13.03 (br, 1H); 7.31-7.19 (m, 3H); 6.97 (d, J=7.4, 2H); 6.95 (br, 1H); 6.70 (d, J=3.8, 1H); 6.67 (dd, J=12.4, 3.9, 1H); 6.28 (dd, J=8.5, 2.6, 1H); 5.39 (ABq, 2H); 4.64 (s, 2H); 3.92 (br, 1H); 2.71 (m, 1H); 2.44 (m, 1H); 2.02 (m, 2H); 1.76 (m, 2H).

Example 52

Preparation of [9-benzyl-5-carbamoyl-1-fluorocarbazol-4-yl]oxyacetic acid

A. Preparation of 9-benzyl-5-carbamoyl-4-methoxy-1-fluorocarbazole

A solution of 0.458 g of 9-benzyl-5-methoxy-8-fluoro-1,2,3,4-tetrahydrocarbazole-4-carboxamide in 13 ml of dry dioxane under nitrogen was treated with 0.59 g of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone and refluxed for one hour. The reaction mixture was cooled and filtered and the precipitate was washed with 15 ml of dioxane. The filtrate and washing were poured into saturated sodium bicarbonate solution and extracted three times with ethyl acetate. The extracts were washed with saturated sodium bicarbonate, with water and then with brine; dried over magnesium sulfate and concentrated. This residue was chromatographed on silica gel using dichloromethane/ 0-2% methanol to afford 0.45 g of subtitle compound. ESIMS *m/e* 349 (M^++1)

Elemental Analyses

Calculated:	C 72.42; H 4.92; N 8.04
Found:	C 72.35; H 4.81; N 7.88

B. Preparation of [9-benzyl-5-carbamoyl-1-fluorocarbazol-4-yl]oxyacetic acid methyl ester

A solution of 0.45 g of 9-benzyl-5-carbamoyl-4-methoxy-1-fluorocarbazole in 25 ml of dichloromethane was cooled in an ice bath treated dropwise with 12 ml of 1.0 M boron tribromide solution in dichloromethane. The reaction was allowed to warm to room temperature slowly over 2 hours and then quenched by pouring into ice and then adding 50 ml of 1 N HCl. The mixture was extracted with dichloromethane

(3x200 ml) and the extracts were dried over magnesium sulfate and concentrated to afford 0.35 g (78%) of the demethylated intermediate. This intermediate (0.215 g) was alkylated and purified similarly to Example GH1, Part D to afford 0.166 g (64%) of the subtitle compound. mp. 190-191°C

Elemental Analyses

Calculated:	C 67.97; H 4.71; N 6.89
Found:	C 67.81; H 4.94; N 6.96

C. Preparation of [9-benzyl-5-carbamoyl-1-fluorocarbazol-4-yl]oxyacetic acid

[9-Benzyl-5-carbamoyl-1-fluorocarbazol-4-yl]oxyacetic acid methyl ester (56 mg) was hydrolyzed and isolated similarly as described in Example 50, Part D to afford 54 mg of the title compound. FDMS *m/e* 392 (M^+); ESIMS *m/e* 393 (M^++1), 391 (M^+-1) NMR (300 MHz, d^6-DMSO): δ 12.92 (br, 1H); 7.70 (m, 2H); 7.45 (t, J=7.5, 1H); 7.39 (br, 1H); 7.28-7.17 (m, 4H); 7.12 (d, J=7.2, 1H); 7.07 (d, J=7.0, 2H); 6.51 (dd, J=8.8, 2.7, 1H); 5.77 (s, 2H); 4.80 (s, 2H).

Elemental Analyses

Calculated:	C 67.34; H 4.37; N 7.14
Found:	C 66.92; H 4.49; N 6.77

Example 53

Preparation of [9-benzyl-4-carbamoyl-8-chloro-1,2,3,4-tetrahydrocarbazol-5-yl]oxyacetic acid

A. Preparation of ethyl 9-benzyl-5-methoxy-8-chloro-1,2,3,4-tetrahydrocarbazole-4-carboxylate

N-benzyl-2-chloro-5-methoxyaniline was prepared similarly to Example 51, Part E. A solution of 2.07 g of N-

benzyl-2-chloro-5-methoxyaniline in 60 ml of dry tetrahydrofuran was converted similarly to Example GH3, Part F and chromatographed on silica gel using 15:1 hexane/ethyl acetate to afford 1.65 g (50%) of the subtitle compound. Ex. 59, A. ESIMS *m/e* 398 (M^++1) NMR (300 MHz, $CDCl_3$): δ 7.29-7.19 (m, 3H); 6.92 (m, 3H); 6.36 (d, J=8.4, 1H); 5.87 (d, J=17.4, 1H); 5.53 (d, J=17.3, 1H); 4.16 m, 3H); 3.81 (s, 3H); 2.66 (dt, J=16.3, 5.4, 1H); 2.49 (dt, J=16.6, 6.6, 1H); 2.05 (m, 2H); 1.98-1.79 (m, 2H); 1.25 (t, 3H).

B. Preparation of 9-benzyl-5-methoxy-8-chloro-1,2,3,4-tetrahydrocarbazole-4-carboxamide

Ethyl 9-benzyl-5-methoxy-8-chloro-1,2,3,4-tetrahydrocarbazole-4-carboxylate (1.65g) was converted similarly to Example 51, Part G to afford 1.54 g (100%) of the subtitle compound. Ex. 59, B. mp. 205-8°C ESIMS *m/e* 369 (M^++1).

C. Preparation of [9-benzyl-4-carbamoyl-8-chloro-1,2,3,4-tetrahydrocarbazol-5-yl]oxyacetic acid methyl ester

9-Benzyl-5-methoxy-8-chloro-1,2,3,4-tetrahydrocarbazole-4-carboxamide (0.405 g) was converted similarly to Example 51, Part H and chromatographed on silica gel using dichlormethane/0-1.5% methanol to afford 0.248 g (53%) of the subtitle compound. Ex. 59, C. m.p. 185-186°C.

Elemental Analyses

Calculated:	C 64.71; H 5.43; N 6.56
Found:	C 64.98; H 5.39; N 6.67

D. Preparation of [9-benzyl-4-carbamoyl-8-chloro-1,2,3,4-tetrahydrocarbazol-5-yl]oxyacetic acid

[9-Benzyl-4-carbamoyl-8-chloro-1,2,3,4-tetrahydrocarbazol-5-yl]oxyacetic acid methyl ester (58 mg) was hydrolyzed similarly as described in Example 49, Part E to afford 54 mg of the title compound. Ex. 59, D. ESIMS *m/e* 413 (M^++1), 411 (M^+-1) NMR (300 MHz, d^6-DMSO): δ 13.05 (br, 1H); 7.30-7.18 (m, 3H); 6.90 (d+m, J=7.6, 4H); 6.73 (br, 1H); 6.39 (d, J=8.3, 1H); 5.77 and 5.58 (ABq, J=17.5, 2H); 4.67 (s, 2H); 3.95 (br, 1H); 2.66 (m, 1H); 2.43 (m, 1H); 2.00 (m, 2H); 1.76 (m, 2H).

Elemental Analyses

Calculated:	C 64.00; H 5.13; N 6.78; Cl 8.59
Found:	C 62.82; H 5.34; N 6.22; Cl 7.99

Example 54

Preparation of [9-benzyl-5-carbamoyl-1-chlorocarbazol-4-yl]oxyacetic acid

A. Preparation of 9-benzyl-5-carbamoyl-4-methoxy-1-chlorocarbazole

A solution of 1.0 g of 9-benzyl-5-methoxy-8-methyl-1,2,3,4-tetrahydrocarbazole-4-carboxamide was oxidized similarly to Example 51, Part A and chromatographed on silica gel using dichloromethane/ 0-1% methanol to afford 0.66 g (67%) of the subtitle compound. FDMS *m/e* 364 (M^+)

Elemental Analyses

Calculated:	C 69.14; H 4.70; N 7.68; Cl 9.72
Found:	C 69.40; H 4.64; N 7.49; Cl 9.98

B. Preparation of 5-carbamoyl-4-hydroxy-1-chlorocarbazole

A solution of 0.66 g of 9-benzyl-5-carbamoyl-4-methoxy-1-chlorocarbazole in 40 ml of dichloromethane was cooled in an ice bath treated dropwise with 14 ml of 1.0 M boron tribromide solution in dichloromethane. The reaction was allowed to warm to room temperature slowly over 2 hours and then quenched by pouring into ice and then adding 50 ml of 1 N HCl. The mixture was extracted with dichloromethane (3x200 ml) and the extracts were washed with brine, dried with magnesium sulfate and concentrated. The aqueous layers exhibited a precipitate and was then extracted twice with ethyl acetate, washed with brine, dried with magnesium sulfate and concentrated to afford 0.287 g of the subtitle compound. The first residue was chromatographed on silica gel using 0.5% methanol in dichloromethane to afford another 93 mg of the subtitle compound. (total yield 80%) ESIMS *m/e* 259 (M^+-1) NMR (300 MHz, d^6-DMSO): δ 11.79 (s, 1H); 10.76 (s, 1H); 8.87 (br s, 1H); 8.41 (br s, 1H); 7.77 (t, J=4.6, 1H); 7.48 (d, J=4.2, 2H); 7.34 (d, J=8.5, 1H); 6.54 (d, J=8.5, 1H).

C. Preparation of [5-carbamoyl-1-chlorocarbazol-4-yl]oxyacetic acid methyl ester

A solution of 0.28 g of 5-carbamoyl-4-hydroxy-1-chlorocarbazole in 6 ml of tetrahydrofuran was added to 0.043 g of sodium hydride (60% in mineral oil) in 1 ml of tetrahydrofuran and stirred for 60 minutes at room temperature. Methyl bromoacetate (0.11 ml) was then added and the reaction was stirred overnight. The reaction mixture was poured into 20 ml of saturated ammonium chloride solution and then extracted twice with ethyl acetate. The extracts were washed with water and then with brine, dried over magnesium sulfate and concentrated. The residue was

chromatographed on silica gel eluting with chloroform and then 2:1 chloroform/ethyl acetate to afford 0.16 g (45%) of the subtitle compound. ESIMS *m/e* 333 (M^++1), 335 (M^++3), 331 (M^+-1) NMR (300 MHz, d^6-DMSO): δ 11.73 (s, 1H); 7.56 (d, J=8.1, 1H); 7.50 (br s, 1H); 7.43-7.35 (m, 2H); 7.18 (br s, 1H); 7.06 (d, J=7.8, 1H); 6.56 (d, J=8.6, 1H); 4.90 (s, 2H); 3.70 (s, 3H).

D. Preparation of [9-benzyl-5-carbamoyl-1-chlorocarbazol-4-yl]oxyacetic acid methyl ester

A solution of 78 mg of [5-carbamoyl-1-chlorocarbazol-4-yl]oxyacetic acid methyl ester in 0.8 ml of dry dimethylformamide was added to 10 mg sodium hydride (60% in mineral oil) in 0.2 ml of dimethylformamide and stirred for 15 minutes. Benzyl bromide (0.031 ml) was then added and the reaction was stirred overnight. The reaction mixture was poured into water and acidified with 1 ml of 1 N HCl solution and extracted twice with ethyl acetate. The extracts were washed with water (3x) and then with brine, dried over magnesium sulfate and concentrated. The residue was chromatographed on silica gel eluting with methanol/0-2% in dichloromethane to afford 40 mg of the subtitle compound. ESIMS *m/e* 423 (M^++1) 425 (M^++3) NMR (300 MHz, $CDCl_3$): δ 7.43-7.22 (m, 7H); 7.06 (d, J=7.3, 2H); 6.51 (d, J=8.6, 1H); 6.05 (s, 2H); 5.80 (br, 2H); 4.88 (s, 2H); 3.83 (s, 3H).

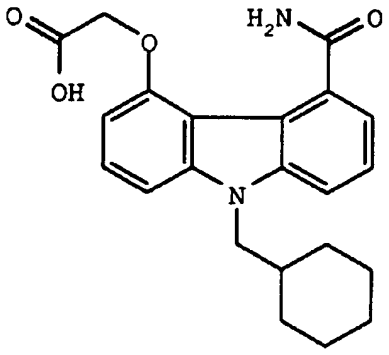
E. Preparation of [9-benzyl-5-carbamoyl-1-chlorocarbazol-4-yl]oxyacetic acid

[9-Benzyl-5-carbamoyl-1-chlorocarbazol-4-yl]oxyacetic acid methyl ester (15 mg) was hydrolyzed similarly as described in Example 50, Part D to afford 14 mg of the title compound. mp. 240-2°C ESIMS *m/e* 409 (M^++1), 411 (M^++3),

407 (M^+-1) NMR (300 MHz, d^6-DMSO): δ 12.94 (br, 1H); 7.70 (br, 1H); 7.61 (d, J=8.3, 1H); 7.43 (t, J=7.8, 1H); 7.36 (m, 2H); 7.28-7.19 (m, 3H); 7.13 (d, J=7.2, 1H); 6.99 (d, J=7.4, 2H); 6.63 (d, J=8.6, 1H); 6.08 (s, 2H); 4.83 (s, 2H).

EXAMPLE 55

Preparation of [9-[(Cyclohexyl)methyl]-5-carbamoylcarbazol-4-yl]oxyacetic acid



A. 9-[(Cyclohexyl)methyl]-5-carbomethoxy-1,2-dihydrocarbazol-4(3H)-one

A 0 °C suspension of 5-carbomethoxy-1,2-dihydro-9H-carbazol-4(3H)-one (1.0 g, 4.11 mmol), a catalytic amount of NaI (ca. 10 mg) and K_2CO_3 (1.1 g, 8.22 mmol) in 10 mL of DMF was treated with cyclohexylmethyl bromide (0.631 mL, 4.52 mmol). After stirring overnight at ambient temperature, an additional 0.63 mL cyclohexylmethylbromide was added, and the resulting mixture was heated at 60 °C for 3 hours. The mixture was poured into H_2O (30 mL) and extracted with EtOAc (2 x 25 mL). The combined organic layers were washed with H_2O (4 x 50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by radial chromatography on silica gel (elution with a gradient of 20% to 40% EtOAc/hexanes) to afford 1.36 g (4.01 mmol; 97%) of

9-[(cyclohexyl)methyl]-5-carbomethoxy-1,2-dihydrocarbazol-4(3H)-one as a white foam. IR ($CHCl_3$, cm^{-1}) 3011, 2932, 2857, 1725, 1649, 1469, 1446, 1288 and 1120. MS (ES) m/e 340 (M+1), 453 ($M+AcO^-$). FAB HRMS m/e, Calcd for $C_{21}H_{26}NO_3$: 340.1913. Found: 340.1916 (M+1).

Elemental Analyses for $C_{21}H_{25}NO_3$:

Calculated: C, 74.31; H, 7.42; N, 4.13.

Found: C, 72.65; H, 7.39; N, 4.70.

B. 9-[(Cyclohexyl)methyl]-4-hydroxy-5-carbomethoxy carbazole

A solution of 9-[(cyclohexyl)methyl]-5-carbomethoxy-1,2-dihydrocarbazol-4(3H)-one (1.16 g, 3.42 mmol) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (853 mg, 3.76 mmol) in 20 mL of toluene was heated at 80 °C for 3 hours. The mixture was purified directly by column chromatography on silica gel (elution with CH_2Cl_2) to afford 259 mg (0.768 mmol; 22%) of 9-[(cyclohexyl)methyl]-4-hydroxy-5-carbomethoxy carbazole as a yellow oil which slowly solidified. MS (ES) m/e 338 (M+1), 336 (M-1).

Elemental Analyses for $C_{21}H_{23}NO_3$:

Calculated: C, 74.75; H, 6.87; N, 4.15.

Found: C, 74.95; H, 6.99; N, 4.42.

C. 9-[(Cyclohexyl)methyl]-4-hydroxy-5-carbamoyl carbazole

A solution of 9-[(cyclohexyl)methyl]-4-hydroxy-5-carbomethoxy carbazole (205 mg, 0.608 mmol) in 5 mL of THF and 20 mL of concentrated aqueous ammonium hydroxide was treated with a stream of NH_3 gas to ensure saturation. The reaction vessel was capped, and the mixture was heated at 35 °C with stirring until tlc indicated complete consumption of starting material (20 hrs). The THF was evaporated, and the aqueous layer was filtered. The green solid precipitate was dissolved in THF and purified by radial chromatography on

silica gel (elution with CH_2Cl_2). The resultant foam was triturated with ether to afford 138 mg (70%) of the title compound as an off-white solid. IR (KBr, cm^{-1}) 3418, 3200, 3131, 1629, 1600, 1443, 1261, 778. 'FAB HRMS m/e, Calcd for $C_{20}H_{23}N_2O_2$: 323.1760. Found: 323.1760 (M+1).

D. [9-[(Cyclohexyl)methyl]-5-carbamoylcarbazol-4-yl]oxyacetic acid, methyl ester

A mixture of 9-[(cyclohexyl)methyl]-4-hydroxy-5-carbamoyl carbazole (60 mg, 0.186 mmol) and Cs_2CO_3 (150 mg; 0.460 mmol) in 2 mL of DMF was treated with methyl bromoacetate (0.023 mL; 0.242 mmol). The reaction was stirred for 2 hours at ambient temperature, then it was diluted with EtOAc and H_2O (10 mL each). The aqueous layer was saturated with solid NaCl and extracted with EtOAc (2 x 10 mL). The combined organic layers were washed with H_2O (2 x 25 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification of the crude residue by flash chromatography on silica gel (elution with a gradient of 0% to 90% EtOAc/hexanes) followed by trituration with Et_2O/EtOAc afforded 45 mg (0.114 mmol; 61%) of title compound as an off-white solid. MS (ES) m/e 395 (M+1), 378 ($M+H-NH_3$), 453 ($M+AcO^-$).

Elemental Analyses for $C_{23}H_{26}N_2O_4 \cdot 0.3H_2O$:

Calculated: C, 69.08; H, 6.71; N, 7.01.

Found: C, 69.13; H, 6.71; N, 7.09.

E. [9-[(Cyclohexyl)methyl]-5-carbamoylcarbazol-4-yl]oxyacetic acid

A slurry of [9-[(cyclohexyl)methyl]-5-carbamoylcarbazol-4-yl]oxyacetic acid, methyl ester (20 mg, 0.051 mmol) in 0.3 mL of THF and 0.1 mL of MeOH was treated with 0.1 mL of 1 N aq LiOH (0.1 mmol), and the mixture

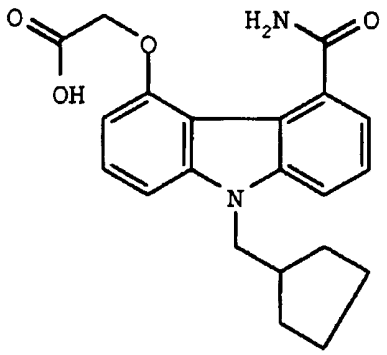
stirred at room temperature for 2 h. The reaction was acidified with 0.2 N HCl, and the organics were removed *in vacuo*. The white precipitate was filtered away from the aqueous layer and rinsed with Et_2O to afford 16 mg (0.042 mmol; 83%) the title acid as a white powder. MS (ES) m/e 381 (M+1), 364 (M+H-NH_3), 379 (M-1).

Elemental Analyses for $C_{22}H_{24}N_2O_4$:

Calculated:	C, 69.46;	H, 6.36; N, 7.36.
Found:	C, 69.34;	H, 6.35; N, 7.29.

EXAMPLE 56

Preparation of [9-[(Cyclopentyl)methyl]-5-carbamoylcarbazol-4-yl]oxyacetic acid



A. 9-[(Cyclopentyl)methyl]-5-carbomethoxy-1,2-dihydrocarbazol-4(3H)-one

A suspension of 5-carbomethoxy-1,2-dihydro-9H-carbazol-4(3H)-one (820 g, 3.37 mmol), a catalytic amount of NaI (ca. 10 mg) and K_2CO_3 (930 mg, 6.74 mmol) in 6 mL of DMF was treated with cyclopentylmethyl chloride (*JOC*, 1964, *29*, 421-423; 400 mg, 3.37 mmol). After stirring overnight at ambient temperature, an additional 800 mg of cyclopentylmethyl chloride and 1 g of NaI were added, and

the resulting mixture was heated at 80 °C overnight. An additional 800 mg of cyclopentylmethyl chloride and 2.2 g of Cs_2CO_3 were added, and the reaction mixture was heated at 80 °C for 24 h. An additional 1.6 g of cyclopentylmethyl chloride was added, and the reaction mixture was heated at 80 °C for 3 d The mixture was poured into H_2O (30 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by radial chromatography on silica gel (elution with gradient of 10% to 40% EtOAc/hexanes) to afford 775 mg (2.38 mmol; 71%) of 9-[(cyclopentyl)methyl]-5-carbomethoxy-1,2-dihydrocarbazol-4(3H)-one as a brown foam. MS (ES) m/e 326 (M+1), 384 ($M+AcO^-$).

Elemental Analyses for $C_{20}H_{23}NO_3$:

Calculated: C, 73.82; H, 7.12; N, 4.30.

Found: C, 74.12; H, 7.21; N, 4.45.

B. 9-[(Cyclopentyl)methyl]-4-hydroxy-5-carbomethoxy carbazole

A solution of 9-[(cyclopentyl)methyl]-5-carbomethoxy-1,2-dihydrocarbazol-4(3H)-one (730 mg, 2.24 mmol) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (560 mg, 2.47 mmol) in 20 mL of toluene was heated at 80 °C for 3 hours. The mixture was purified directly by column chromatography on silica gel (elution with CH_2Cl_2) to afford 140 mg (0.433 mmol; 19%) of 9-[(cyclopentyl)methyl]-4-hydroxy-5-carbomethoxy carbazole as a yellow oil which slowly solidified. MS (ES) m/e 324 (M+1), 322 (M-1).

Elemental Analyses for $C_{20}H_{21}NO_3 \cdot 0.3H_2O$:

Calculated: C, 73.06; H, 6.62; N, 4.26.

Found: C, 73.19; H, 6.44; N, 4.40.

C. 9-[(Cyclopentyl)methyl]-4-hydroxy-5-carbamoyl carbazole

A solution of 9-[(cyclopentyl)methyl]-4-hydroxy-5-carbomethoxy carbazole (110 mg, 0.34 mmol) in 3 mL of THF and 20 mL ofconcentrated aqueous ammonium hydroxide was treated with a stream of NH_3 gas to ensure saturation. The reaction vessel was capped, and the mixture heated to 35 °C with stirring until tlc indicated complete consumption of starting material (20 h). The THF was evaporated, and the aqueous layer was filtered. The resultant solid was triturated with ether to afford 50 mg (0.162; 48%) of the title compound as a greenish-white solid. IR (KBr, cm^{-1}) 3416, 3199, 3126, 1630, 1599. 1442, 1262, 778. 'FAB HRMS m/e, Calcd for $C_{20}H_{21}N_2O_2$: 309.1603. Found: 309.1607 (M+1).'

D. [9-[(Cyclopentyl)methyl]-5-carbamoylcarbazol-4-yl]oxyacetic acid, methyl ester

A mixture of 9-[(cyclopentyl)methyl]-4-hydroxy-5-carbamoyl carbazole (45 mg, 0.146 mmol) and Cs_2CO_3 (120 mg; 0.365 mmol) in 2 mL of DMF was treated with methyl bromoacetate (0.018 mL; 0.19 mmol). The reaction was stirred for 2 hours at ambient temperature, then it was diluted with EtOAc and H_2O (10 mL each). The aqueous layer was saturated with solid NaCl extracted with EtOAc (2 x 10 mL). The combined organic layers were washed with H_2O (2 x 25 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification of the crude residue by flash chromatography on silica gel (elution with a gradient of 0% to 100% EtOAc/hexanes) followed by trituration with Et_2O/EtOAc afforded 26 mg (0.0683 mmol; 47%) of title compound as a tan solid. MS (ES) m/e 381 (M+1), 364 (M+H-NH_3), 439 (M+AcO^-).

Elemental Analyses for $C_{23}H_{26}N_2O_4 \cdot 0.1H_2O$:

Calculated: C, 69.13; H, 6.38; N, 7.33.
Found: C, 68.99; H, 6.39; N, 7.41.

E. [9-[(Cyclopentyl)methyl]-5-carbamoylcarbazol-4-yl]oxyacetic acid

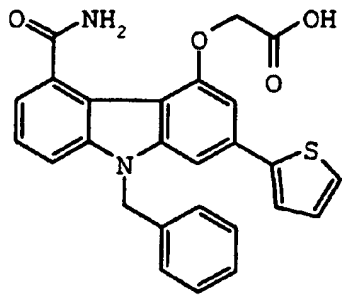
A slurry of [9-[(cyclopentyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, methyl ester (20 mg, 0.065 mmol) in 0.3 mL of THF and 0.1 mL of MeOH was treated with 0.1 mL of 1 N aq LiOH (0.1 mmol), and the mixture stirred at room temperature for 2 hours. The reaction was acidified with 0.2 N HCl, and the organics were removed *in vacuo*. The white precipitate was filtered away from the aqueous layer and rinsed with Et_2O to afford 15 mg (0.0409 mmol; 63%) the title acid as a white powder. MS (ES) m/e 367 (M+1), 350 (M+H-NH_3), 365 (M-1).

Elemental Analyses for $C_{21}H_{22}N_2O_4 \cdot 0.3H_2O$:

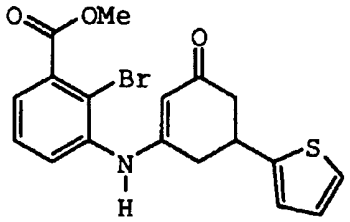
Calculated: C, 67.84; H, 6.13; N, 7.53.
Found: C, 67.73; H, 5.97; N, 7.70.

Example 57

[5-carbamoyl-9-(phenylmethyl)-2-(2-thienyl)carbazol-4-yl]oxyacetic acid

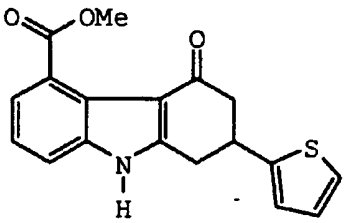


A. Preparation of 3-(2-bromo-3-carbomethoxyanilino)-5-(2-thienyl)cyclohex-2-en-1-one



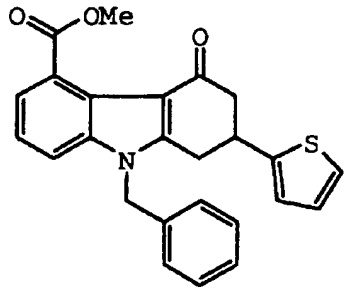
Prepared in 59% yield by the method of Example 17C. ^{1}H-NMR ($CDCl_3$): δ 2.63 (dd, J = 16.5, 118. Hz, 1H), 2.78-2.96 (m, 3H), 3.71-3.80 (m, 1H), 3.94 (s, 3H), 5.61 (s, 1H), 6.23 (br s, 1H), 6.93 (d, J = 3.5 Hz, 1H), 6.97-6.99 (m, 1H), 7.21 (d, J = 5.2 Hz, 1H), 7.34 (br t, J = 7.8 Hz, 1H), 7.55 (d, J = 7.8 Hz, 2H).

B. Preparation of 5-carbomethoxy-1,2-dihydro-2-(2-thienyl)-9H-carbazol-4(3H)-one



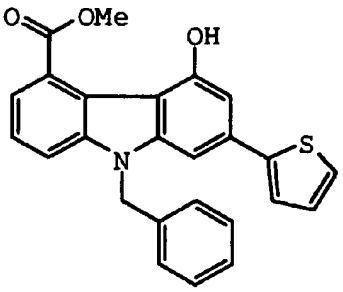
Prepared in 85% yield by the method of Example 17D. ^{1}H-NMR ($CDCl_3$): δ 2.73 (dd, J = 16.3, 11.8 Hz, 1H), 2.91 (dd, J = 16.4, 4.0 Hz, 1H), 3.03 (dd, J = 16.6, 10.8 Hz, 1H), 3.24 (dd, J = 16.6, 4.5 Hz, 1H), 3.75-3.78 (m, 1H), 4.03 (s, 3H), 6.88 (br s, 1H), 6.93-6.96 (m, 1H), 7.17 (d, J = 5.0 Hz, 1H), 7.22-7.26 (m, 1H), 7.36 (d, J = 7.4 Hz, 1H), 7.40 (d, J = 8.0 Hz, 1H),9.17 (br s, 1H).

C. Preparation of 5-carbomethoxy-1,2-dihydro-9-(phenylmethyl)-2-(2-thienyl)carbazol-4(3H)-one



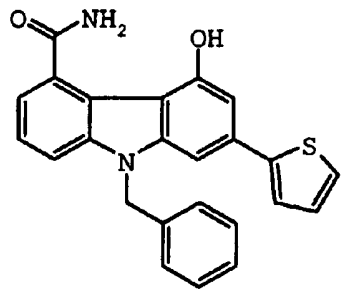
Prepared in 88% yield by the method of Example 17E. ^{1}H-NMR ($CDCl_3$): δ 2.84 (dd, J = 16.5, 11.6 Hz, 1H), 2.97-3.10 (m, 2H), 3.34 (dd, J = 16.5, 4.5 Hz, 1H), 3.89-3.96 (m, 1H), 4.06 (s, 3H), 5.38 (s, 2H), 6.89-7.00 (m, 4H), 7.18 (d, J = 5.3 Hz, 1H), 7.25-7.41 (m, 6H).

D. Preparation of 5-carbomethoxy-4-hydroxy-9-(phenylmethyl)-2-(2-thienyl)carbazole



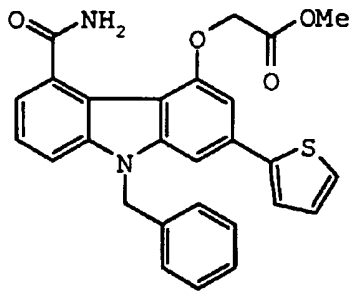
Prepared in 76% yield by the method (b) of Example 17F. ^{1}H-NMR ($CDCl_3$): δ 4.11 (s, 3H), 5.55 (s, 2H), 7.07-7.12 (m, 3H), 7.16 (s, 2H), 7.24-7.30 (m, 4H), 7.37-7.42 (m, 2H), 7.56 (d, J = 8.1 Hz, 1H), 8.01 (d, J = 7.6 Hz, 1H).

E. Preparation of 5-carbamoyl-4-hydroxy-9-(phenylmethyl)-2-(2-thienyl)carbazole



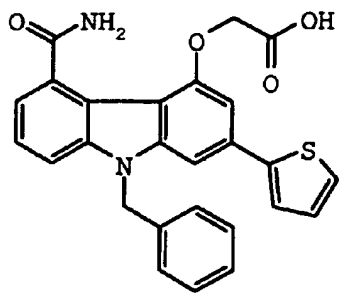
Prepared in 85% yield by the method of Example 17G. ^{1}H-NMR (DMSO-d_6): δ 5.73 (s, 2H), 6.87 (s, 1H), 7.08-7.26 (m, 6H), 7.41-7.56 (m, 5H), 7.76 (br t, J = 4.5 Hz, 1H), 8.39 (s, 1H), 8.83 (s, 1H), 10.76 (s, 1H).

F. Preparation of [5-carbamoyl-9-(phenylmethyl)-2-(2-thienyl)carbazol-4-yl]oxyacetic acid, methyl ester



Prepared in 92% yield by the method of Example 17H. ^{1}H-NMR (DMSO-d_6): δ 3.70 (s, 3H), 4.99 (s, 2H), 5.71 (s, 2H), 6.85 (s, 1H), 7.04 (d, J = 7.2 Hz, 1H), 7.11-7.26 (m, 7H), 7.35 (br t, J = 7.7 Hz, 1H), 7.50-7.57 (m, 5H).

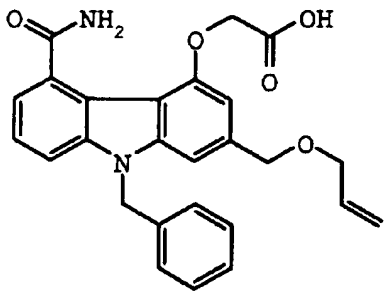
G. Preparation of [5-carbamoyl-9-(phenylmethyl)-2-(2-thienyl)carbazol-4-yl]oxyacetic acid



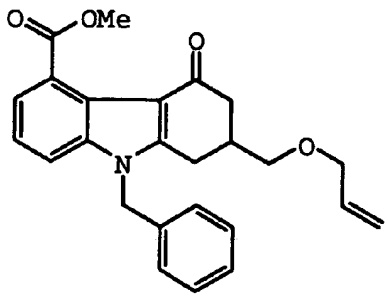
Prepared in 98% yield by the method of Example 17I. ^{1}H-NMR (DMSO-d_6): δ 4.90 (s, 2H), 5.72 (s, 2H), 6.85 (s, 1H), 7.04-7.26 (m, 7H), 7.33-7.38 (m, 2H), 7.50-7.59 (m, 4H), 7.71 (s, 1H), 12.99 (br s, 1H).

Example 58

[5-carbamoyl-9-(phenylmethyl)-2-[[(propen-3-yl)oxy]methyl]carbazol-4-yl]oxyacetic acid



A. Preparation of 5-carbomethoxy-1,2-dihydro-9-(phenylmethyl)-2-[[(propen-3-yl)oxy]methyl]carbazol-4(3H)-one

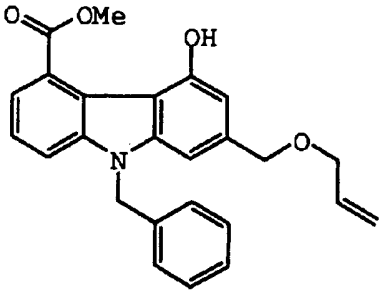


Sodium hydride (63.4 mg, 1.58 mmol) was added to a stirred anhydrous DMF (7 mL) solution containing the compound of Example 19C (480 mg, 1.32 mmol) and allyl bromide (0.172 mL, 1.98 mmol) under a nitrogen atmosphere. The resultant solution was stirred at ambient temperature for 2 hours. Then the mixture was treated with two drops of acetic acid before it was concentrated in vacuo. The residue was subject to chromatography on silica (gradient 30-70% ethyl acetate in hexane) to provide the subtitled compound (395 mg, 74%) as a white solid. IR (KBr) 1726, 1654 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 2.40 (dd, J = 16.5, 11.1 Hz, 1H), 2.57-2.78 (m, 3H), 3.01-3.08 (m, 1H), 3.41 (dd, J = 9.2, 6.9 Hz, 1H), 3.49 (dd, J = 9.2, 4.3 Hz, 1H), 3.95 (d, J = 5.4 Hz, 2H, $-CH_2O-$), 4.04 (s, 3H, $-OCH_3$), 5.14-5.27 (m, 2H, $=CH_2$), 5.32 (s, 2H, $-NCH_2-$), 5.80-5.92 (m, 1H, -CH=), 6.97-7.02 (m, 2H), 7.20-7.39 (m, 6H); ESIMS m/e 404 (M^++1); Elemental Analyses for $C_{25}H_{25}NO_4$:

Calculated: C, 74.42; H, 6.25.

Found: C, 74.59; H, 6.07.

B. Preparation of 5-carbomethoxy-4-hydroxy-9-(phenylmethyl)-2-[[(propen-3-yl)oxy]methyl]carbazole



Prepared in a 78% yield by the method (b) of Example 17F. IR ($CHCl_3$) 3200 (br), 1687 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 4.04 (d, J = 5.7 Hz, 2H, $-CH_2O-$), 4.11 (s, 3H, $-OCH_3$), 4.63 (s, 2H, $-OCH_2-$), 5.15-5.31 (m, 2H, $=CH_2$), 5.55 (s, 2H, $-NCH_2-$), 5.88-6.02 (m, 1H, -CH=), 6.81 (s, 1H), 6.99 (s, 1H), 7.05-

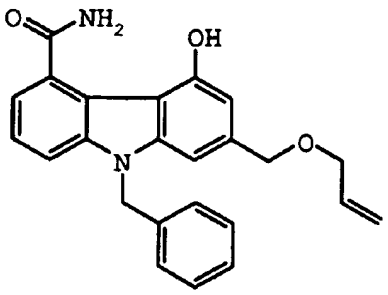
7.09 (m, 2H), 7.22-7.30 (m, 3H), 7.40 (br t, J = 8.0 Hz, 1H), 7.58 (d, J = 8.0 Hz, 1H), 8.00 (d, J = 8.0 Hz, 1H), 10.48 (s, 1H, -OH); ESIMS m/e 402 (M^++1);

Elemental Analyses for $C_{25}H_{23}NO_4$:

Calculated: C, 74.80; H, 5.77.

Found: C, 75.08; H, 5.78.

C. Preparation of 5-carbamoyl-4-hydroxy-9-(phenylmethyl)-2-[[(propen-3-yl)oxy]methyl]carbazole



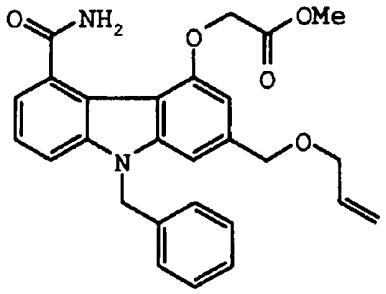
Prepared in a 75% yield by the method of Example 17G. IR (KBr) 3420, 3203 (br), 3121, 1632, 1601 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 3.95 (d, J = 5.3 Hz, 2H, $-CH_2O-$), 4.50 (s, 2H, $-OCH_2-$), 5.08-5.25 (m, 2H, $=CH_2$), 5.65 (s, 2H, $-NCH_2-$), 5.83-5.93 (m, 1H, -CH=), 6.54 (s, 1H), 7.02-7.05 (m, 3H), 7.14-7.25 (m, 3H), 7.39-7.45 (m, 2H), 7.73-7.77 (m, 1H), 8.34 (s, 1H, -NH), 8.79 (s, 1H, -NH), 10.53 (s, 1H, -OH); ESIMS m/e 387 (M^++1);

Elemental Analyses for $C_{24}H_{22}N_2O_3$:

Calculated: C, 74.59; H, 5.74.

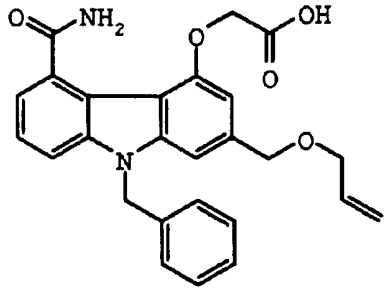
Found: C, 74.85; H, 5.93.

D. Preparation of [5-carbamoyl-9-(phenylmethyl)-2-[[(propen-3-yl)oxy]methyl]carbazol-4-yl]oxyacetic acid, methyl ester



Prepared in a 90% yield by the method of Example 17H. IR (KBr) 3360, 3167, 1758, 1639 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 3.83 (s, 3H, $-OCH_3$), 4.00 (d, J = 5.7 Hz, 2H, $-CH_2O-$), 4.62 (s, 2H, $-OCH_2-$), 4.91 (s, 2H, $-OCH_2-$), 5.16-5.30 (m, 2H, $=CH_2$), 5.52 (s, 2H, $-NCH_2-$), 5.88-6.00 (m, 1H, $-CH=$), 6.05 (br s, 2H, $-NH_2$), 6.59 (s, 1H), 7.05 (s, 1H), 7.06-7.10 (m, 2H), 7.22-7.41 (m, 6H); ESIMS m/e 459 (M^++1).

E. Preparation of [5-carbamoyl-9-(phenylmethyl)-2-[[(propen-3-yl)oxy]methyl]carbazol-4-yl]oxyacetic acid



Prepared in a 89% yield by the method of Example 17I. IR (KBr) 3453, 3421, 3332, 3220, 2580 (br), 1740, 1724, 1631 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 3.95 (d, J = 4.7 Hz, 2H, $-CH_2O-$), 4.53 (s, 2H, $-OCH_2-$), 4.79 (s, 2H, $-OCH_2-$), 5.10-5.26 (m, 2H, $=CH_2$), 5.64 (s, 2H, $-NCH_2-$), 5.80-6.00 (m, 1H, $-CH=$), 6.56 (s, 1H), 7.04-7.40 (m, 9H), 7.57 (d, J = 8.1 Hz, 1H),

7.70 (s, 1H, -NH), 12.94 (br s, 1H, $-CO_2H$); ESIMS m/e 445 (M^++1);

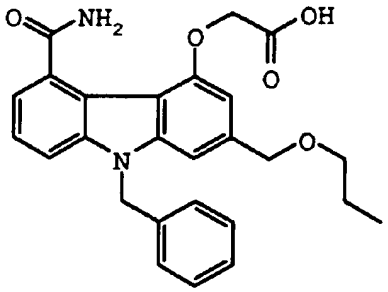
Elemental Analyses for $C_{26}H_{24}N_2O_5$:

Calculated: C, 70.26; H, 5.44.

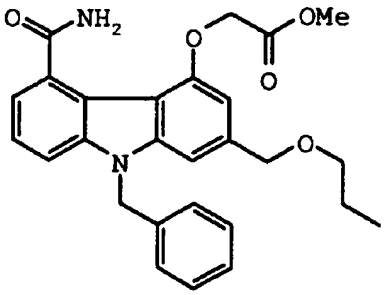
Found: C, 70.00; H, 5.42.

Example 59

[5-carbamoyl-9-(phenylmethyl)-2-[(propyloxy)methyl]carbazol-4-yl]oxyacetic acid



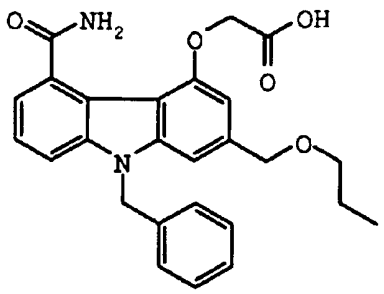
A. Preparation of [5-carbamoyl-9-(phenylmethyl)-2-[(propyloxy)methyl]carbazol-4-yl]oxyacetic acid, methyl ester



Platinum oxide (30 mg) was added to a stirred THF (30 mL) solution containing the compound of Example IID (120 mg, 0.262 mmol) under a nitrogen atmosphere. The mixture was then stirred under a hydrogen atmosphere for 30 minutes. After filtration and concentration, the residue was chromatographed on silica (gradient 0-6% methanol in

methylene chloride) to afford the subtitled compound (117 mg, 97%) as a white solid. IR (KBr) 3364, 3166, 1758, 1742, 1642 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 0.91 (t, J = 7.4 Hz, 3H, $-CH_3$), 1.57-1.65 (m, 2H), 3.40 (t, J = 6.6 Hz, 2H, $-OCH_2-$), 3.83 (s, 3H, $-OCH_3$), 4.60 (s, 2H, $-OCH_2-$), 4.91 (s, 2H, $-OCH_2-$), 5.52 (s, 2H, $-NCH_2-$), 5.95 (br s, 1H, -NH), 6.06 (br s, 1H, -NH), 6.58 (s, 1H), 7.04 (s, 1H), 7.07-7.10 (m, 2H), 7.20-7.41 (m, 6H); ESIMS m/e 461 (M^++1).

B. Preparation of [5-carbamoyl-9-(phenylmethyl)-2-[(propyloxy)methyl]carbazol-4-yl]oxyacetic acid



Prepared in a 99% yield by the method of Example 17I. IR (KBr) 3458, 3413, 3332, 3232, 2500 (br), 1716, 1627 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 0.82 (t, J = 7.3 Hz, 3H, $-CH_3$), 1.45-1.53 (m, 2H), 3.33 (t, J = 6.3 Hz, 2H, $-OCH_2-$), 4.51 (s, 2H, $-CH_2O-$), 4.78 (s, 2H, $-OCH_2-$), 5.64 (s, 2H, $-NCH_2-$), 6.54 (s, 1H), 7.03-7.39 (m, 9H), 7.57 (d, J = 8.2 Hz, 1H), 7.70 (s, 1H, -NH), 12.93 (s, 1H, $-CO_2H$); ESIMS m/e 447 (M^++1);

Elemental Analyses for $C_{26}H_{26}N_2O_5$:

Calculated: C, 69.94; H, 5.87.

Found: C, 70.00; H, 5.88.

Example 60

Preparation of 9-benzyl-7-methoxy-5-((carboxamidomethyl)oxy)-1,2,3,4-tetrahydrocarbazole-4-carboxamide

To 195mg (0.5mmol) of 9-benzyl-7-methoxy-5-cyanomethyloxy-1,2,3,4-tetrahydrocarbazole-4-carboxamide in 3ml CH_2Cl_2 was added 34mg (0.1mmol) tetrabutylammonium sulfate. After cooling to 0°C, 0.25ml 30% H_2O_2 and 3ml 20% NaOH were added. The reaction was allowed to warm to room temperature and stirred for 18h. The mixture was diluted with CH_2Cl_2, washed with water, washed with brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue was chromatographed on silica gel eluting with a gradient of 2 to 10% isopropanol in methylene chloride to give the titled product (36.7mg 19%). An analytical sample was crystallized from methanol.

MS (ES+) 408

Elemental analysis for $C_{23}H_{25}N_3O_4$:

Calculated:	C 67.80;	H 6.18; N 10.31
Theory:	C 67.91;	H 6.17; N 10.44

Example 61

Preparation of 9-benzyl-7-methoxy-5-cyanomethyloxy-carbazole-4-carboxamide

To a stirred solution of 9-benzyl-5-hydroxy-7-methoxycarbazole-4-carboxamide (0.75g, 2.17mmol) in DMF (76ml) and THF (16ml) and added 60% NaH (0.11g, 2.71mmol). After 15 min bromoacetonitrile (0.20ml, 2.93mmol) was added and the reaction was allowed to stir for 4h. The reaction was diluted with EtOAc, extracted with water, then brine, dried (Na_2SO_4), and chromatographed on silica gel using a

CH_2Cl_2-EtOAc-methanol gradient to give the titled compound (0.52g, 63%). MS (ES+) 386

Elemental analysis for $C_{23}H_{19}N_3O_3$:

Calculated:	C 71.68;	H 4.97; N 10.90
Theory:	C 71.67;	H 4.72; N 10.65

Example 62 424805

Preparation of 9-benzyl-7-methoxy-5-((1H-tetrazol-5-yl-methyl)oxy)-carbazole-4-carboxamide

0.20gram (0.52mmol) of 9-benzyl-7-methoxy-5-cyanomethyloxy-carbazole-4-carboxamide was heated with 2.2ml tri-n-butyl tin hydride at 95°C for 3.5 h. The reaction was then added to a mixture of 56 ml acetonitrile, 11ml tetrahydrofuran, and 22ml acetic acid and stirred for 2 h. The mixture was extracted 4 times with hexane and the residue evaporated *in vacuo*. The residue was chromatographed on silica gel using a CH_2Cl_2-methanol gradient, then 1% HOAc in EtOAc. Crystallization from acetone and hexane afforded the titled compound (0.047g, 21%). MS (ES+) 412, 429

Elemental analysis for $C_{23}H_{24}N_6O_3$:

Calculated:	C 64.48;	H 4.71; N 19.61
Theory:	C 64.58;	H 4.67; N 19.68

Example 63

Preparation of 9-benzyl-7-methoxy-5-((carboxamidomethyl)oxy)-carbazole-4-carboxamide

To 200mg (0.52mmol) of 9-benzyl-7-methoxy-5-cyanomethyloxy-carbazole-4-carboxamide in 6ml CH_2Cl_2 was added 35mg (0.1mmol) tetrabutylammonium sulfate. After cooling to 0°C, 0.26ml 30% H_2O_2 and 6ml 20% NaOH. were added.

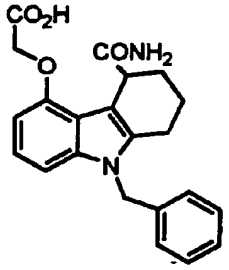
The reaction was allowed to warm to room temperature and stirred for 18h. The mixture was diluted with CH_2Cl_2 and methanol, washed with water, washed with brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue was chromatographed on silica gel using a CH_2Cl_2-ethanol gradient. Crystallization from methanol afforded the titled compound (22.5mg, 11%). MS (FD) 403

Elemental analysis for $C_{23}H_{21}N_3O_4$:

Calculated:	C 68.47;	H 5.25; N 10.42
Theory:	C 68.65;	H 4.99; N 10.40

Example 64

Preparation of [9-Benzyl-4-carbamoyl-1,2,3,4-tetrahydrocarbaole-5-yl]oxyacetic acid



A. 9-Benzyl-4-carboxy-5-methoxy-1,2,3,4-tetrahydrocarbazole, Ethyl Ester.

A solution of 1.50 g (4.02 mmol) of 9-Benzyl-4-carboxy-8-chloro-5-methoxy-1,2,3,4-tetrahydrocarbazole, ethyl ester and 0.45 g (4.40 mmol) of Et_3N in 25 mL of EtOH was treated with 0.24 g of 5% Pd-C and the mixture hydrogenated at 60 psi for 16 hrs. The reaction was filtered and concentrated in vacuo to give 1.40 g of a tan solid. ^1H NMR ($CDCl_3$) δ 7.30-7.19 (m, 3H), 7.03-6.95 (m, 3H), 6.80 (d, 1H, J=8.1 Hz), 6.44 (d, 1H, J=7.7 Hz), 5.22 (d, 2H, J=5.9 Hz), 4.22-4.11 (m, 3H), 3.82 (s, 3H), 2.75-2.64 (m, 1H), 2.59-2.48 (m, 1H), 2.11-1.64 (m, 4H), and 1.25

(t, 3H, J=7.0 Hz). IR ($CHCl_3$) 2959, 1725, 1499, 1453, 1260, 1178, 1128 cm-1;

Elemental Analysis for $C_{23}H_{25}NO_3$:

Calculated: 363.1836

Found: 363.1834.

B. 9-Benzyl-4-carbamoyl-5-hydroxy-1,2,3,4-tetrahydrocarbazole.

A 0 °C solution of 1.00 g (2.80 mmol) 9-benzyl-4-carboxy-5-methoxy-1,2,3,4-tetrahydrocarbazole, ethyl ester in 15 mL of CH_2Cl_2 was treated with 22.40 mL (22.40 mmol; 1M in CH_2Cl_2) of BBr_3. The cold bath was removed and the reaction stirred until tlc analysis (10% EtOAc in hexanes) indicated complete consumption of starting material (1.5 hrs). The reaction was cooled to 0 °C and was quenched with 5.0 mL of MeOH. The mixture was stirred at ambient temperature for 18 hrs and was concentrated *in vacuo*. The black oil was taken up in 200 mL of CH_2Cl_2 and the solution washed with H20 (100 mL) and sat'd aq $NaHCO_3$ (100mL). Evaporation of the solvent *in vacuo* afforded 700 mg of a black oil. Purification by radial chromatography (10 % EtOAc in hexanes) afforded 400 mg of 9-benzyl-4-carboxy-5-hydroxy-1,2,3,4-tetrahydrocarbazole, ethyl ester which was taken on directly to the next reaction.

The phenol was taken up in 40 ml of THF and the solution treated with 10 mL of NH_4OH. The reaction vessel was capped and the mixture stirred vigorously for 13 days. The reaction was poured into H_2O and the mixture extracted with EtOAc (3 x 150 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo* to give 300 mg of a brown foam. Radial chromatography (3% MeOH in CH_2Cl_2) afforded 50 mg of starting phenol and 80 mg (0.03 mmol; 22 %) of 9-benzyl-4-carbamoyl-5-hydroxy-1,2,3,4-tetrahydrocarbazole. ^1H NMR ($CDCl_3$) δ 7.33-7.24 (m, 3H),

7.06-6.97 (m, 3H), 6.81 (d, 1H, J=8.1 Hz), 6.56 (d, 1H, J=7.5 Hz), 5.22 (d, 2H, J=2.2 Hz), 4.20-4.15 (m, 1H), 2.78-2.67 (m, 1H), 2.63-2.51 (m, 1H), 2.35-2.27 (m, 1H), and 2.09-1.91 (m, 3H), no phenol proton detected. IR (CHCl3) 3007, 1667, 1586, 1567, 1496, 1266 cm-1;

Elemental Analysis for $C_{20}H_{21}N_2O_2$:

Calculated: 321.1603.

Found: 321.1607.

C. [9-Benzyl-4-carbamoyl-1,2,3,4-tetrahydrocarbaole-5-yl]oxyacetic acid, Methyl Ester.

A solution of 80 mg (0.25 mmol) of 9-benzyl-4-carbamoyl-5-hydroxy-1,2,3,4-tetrahydrocarbazole in 2.5 mL of DMF was treated with 61 mg (0.30 mmol) of Cs_2CO_3 followed by 26 mg (0.30 mmol) of methyl bromoacetate. The mixture was stirred at room temperature until tlc indicated complete consumption of starting material (2 hrs). The reaction was diluted with H_2O (10 mL) and was extracted with EtOAc (3x10 mL). The combined organic layers were washed with H_2O (3 x2 0 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by radial chromatography (SiO_2; 2.5% MeOH in CH_2Cl_2) to afford 50 mg (0.13 mmol; 51%) of [9-benzyl-4-carbamoyl-1,2,3,4-tetrahydrocarbaole-5-yl]oxyacetic acid, methyl ester as an oil. ^1H NMR ($CDCl_3$) δ 7.33-7.21 (m, 3H), 7.05-6.98 (m, 3H), 6.98 (d, 1H, J=7.4 Hz), 6.46 (br s, 1H), 6.37 (d, 1H, J=7.7 Hz), 5.52 (br s, 1H), 5.23 (d, 1H, J=4.9 Hz) 4.79-4.70 (m, 2H), 4.20-4.15 (m, 1H), 3.81 (s, 3H), 2.79-2.69 (m, 1H), 2.63-2.49 (m, 1H), 2.43-2.35 (m, 1H), 2.25-2.09 (m, 1H), and 1.99-1.78 (m, 2H). IR ($CHCl_3$, cm^{-1}) 1759, 1670, 1497, 1453, 1440, and 1132. MS (ES) m/e 393 (M+1).

Elemental Analysis for $C_{23}H_{24}N_2O_4$:

Calculated: C, 70.39; H, 6.16; N, 7.14.

Found: C, 70.29; H, 6.31; N, 7.08.

D. [9-Benzyl-4-carbamoyl-1,2,3,4-tetrahydrocarbaole-5-yl]oxyacetic acid

A solution of 30 mg (0.076 mmol) of [9-benzyl-4-carbamoyl-1,2,3,4-tetrahydrocarbaole-5-yl]oxyacetic acid, methyl ester in 1.0 mL of THF and 1.0 mL of MeOH was treated with 0.2 mL of 1 N aq LiOH (0.2 mmol). The mixture was stirred for 18 hrs. An additional 0.2 mL of 1 N aq LiOH (0.2 mmol) was added and stirring continued. After 1 hr, the mixture was concentrated *in vacuo*. The residue was dissolved in 2.0 mL of H_2O and the solution acidified with 0.2 N aq HCl. The solid was filtered and dried to afford 25 mg of [9-benzyl-4-carbamoyl-1,2,3,4-tetrahydrocarbaole-5-yl]oxyacetic acid as a white solid. ^{1}H NMR (DMSO-d6) δ 7.36-7.12 (m, 5H), 7.05-6.83 (m, 5H), 6.71 (br s, 1H), 6.35 (d, 1H, J=7.6 Hz), 5.27 (s, 2H), 4.64 (s, 2H), 3.93-3.84 (m, 2H), 2.75-2.64 (m, 1H), 2.16-1.95 (m, 2H), 1.81-1.64 (m, 2H) and 1 proton masked by H_2O peak between 2.58-2.40. IR (KBr, cm^{-1}) 3435, 2936, 1722, 1644, 1586, 1566, 1495, 1451, 1354, 1227, 1134, 730, 716, and 698. MS (ES) m/e 377 (M-1) and 379 (M+1).

Elemental Analysis for $C_{22}H_{22}N_2O_4$:

Calculated:	C, 69.83; H, 5.86; N, 7.40.
Found:	C, 70.11; H, 5.76; N, 7.12.

The compounds described herein are believed to achieve their beneficial therapeutic action principally by direct inhibition of human $sPLA_2$, and not by acting as antagonists for arachidonic acid, nor other active agents below arachidonic acid in the arachidonic acid cascade, such as 5-lipoxygenases, cyclooxygenases, etc.

The method of the invention for inhibiting $sPLA_2$ mediated release of fatty acids comprises contacting $sPLA_2$ with an therapeutically effective amount of the compound of Formula (I) or its salt.

The compounds of the invention may be used in a method of treating a mammal (e.g., a human) to alleviate the pathological effects of septic shock, adult respiratory distress syndrome, pancreatitus, trauma, bronchial asthma, allergic rhinitis, and rheumatoid arthritis; wherein the method comprises administering to the mammal a compound of formula (I) in a therapeutically effective amount. A "therapeutically effective" amount is an amount sufficient to inhibit $sPLA_2$ mediated release of fatty acid and to thereby inhibit or prevent the arachidonic acid cascade and its deleterious products. The therapeutic amount of compound of the invention needed to inhibit $sPLA_2$ may be readily determined by taking a sample of body fluid and assaying it for $sPLA_2$ content by conventional methods.

Throughout this document, the person or animal to be treated will be described as a "mammal", and it will be understood that the most preferred subject is a human. However it must be noted that the study of adverse conditions of the central nervous system in non-human animals is only now beginning, an that some instances of such treatments are coming into use. Accordingly, use of the present compounds in non-human animals is contemplated. It will be understood that the dosage

ranges for other animals will necessarily be quite different from the doses administered to humans, and accordingly that the dosage ranges described be recalculated. For example, a small dog may be only 1/10th of a typical human's size, and it will therefore be necessary for a much smaller dose to be used. The determination of an effective amount for a certain non-human animal is carried out in the same manner described below in the case of humans, and veterinarians are well accustomed to such determinations.

As previously noted the compounds of this invention are useful for inhibiting sPLA$_2$ mediated release of fatty acids such as arachidonic acid. By the term, "inhibiting" is meant the prevention or therapeutically significant reduction in release of sPLA$_2$ initiated fatty acids by the compounds of the invention. By "pharmaceutically acceptable" it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

In general, the compounds of the invention are most desirably administered at a dose that will generally afford effective results without causing any serious side effects and can be administered either as a single unit dose, or if desired, the dosage may be divided into convenient subunits administered at suitable times throughout the day.

The specific dose of a compound administered according to this invention to obtain therapeutic or prophylactic effects will, of course, be determined by the particular circumstances surrounding the case, including, for example, the route of administration, the age, weight and response of the individual patient, the condition

being treated and the severity of the patient's symptoms. Typical daily doses will contain a non-toxic dosage level of from about 0.01 mg/kg to about 50 mg/kg of body weight of an active compound of this invention.

Preferably the pharmaceutical formulation is in unit dosage form. The unit dosage form can be a capsule or tablet itself, or the appropriate number of any of these. The quantity of active ingredient in a unit dose of composition may be varied or adjusted from about 0.1 to about 1000 milligrams or more according to the particular treatment involved. It may be appreciated that it may be necessary to make routine variations to the dosage depending on the age and condition of the patient. The dosage will also depend on the route of administration.

A "chronic" condition means a deteriorating condition of slow progress and long continuance. As such, it is treated when it is diagnosed and continued throughout the course of the disease. An "acute" condition is an exacerbation of short course followed by a period of remission. In an acute event, compound is administered at the onset of symptoms and discontinued when the symptoms disappear.

Pancreatitis, trauma-induced shock, bronchial asthma, allergic rhinitis and rheumatoid arthritis may occur as an acute event or a chronic event. Thus, the treatment of these conditions contemplates both acute and chronic forms. Septic shock and adult respiratory distress, on the other hand, are acute conditions treated when diagnosed.

The compound can be administered by a variety of routes including oral, aerosol, rectal, transdermal, subcutaneous, intravenous, intramuscular, and intranasal.

Pharmaceutical formulations of the invention are prepared by combining (e.g., mixing) a therapeutically

effective amount of the compounds of the invention together with a pharmaceutically acceptable carrier or diluent therefor. The present pharmaceutical formulations are prepared by known procedures using well known and readily available ingredients.

In making the compositions of the present invention, the active ingredient will usually be admixed with a carrier, or diluted by a carrier, or enclosed within a carrier which may be in the form of a capsule, sachet, paper or other container. When the carrier serves as a diluent, it may be a solid, semi-solid or liquid material which acts as a vehicle, or can be in the form of tablets, pills, powders, lozenges, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), or ointment, containing, for example, up to 10% by weight of the active compound. The compounds of the present invention are preferably formulated prior to administration.

For the pharmaceutical formulations any suitable carrier known in the art can be used. In such a formulation, the carrier may be a solid, liquid, or mixture of a solid and a liquid. Solid form formulations include powders, tablets and capsules. A solid carrier can be one or more substances which may also act as flavoring agents, lubricants, solubilisers, suspending agents, binders, tablet disintegrating agents and encapsulating material.

Tablets for oral administration may contain suitable excipients such as calcium carbonate, sodium carbonate, lactose, calcium phosphate, together with disintegrating agents, such as maize, starch, or alginic acid, and/or binding agents, for example, gelatin or acacia, and lubricating agents such as magnesium stearate, stearic acid, or talc.

In powders the carrier is a finely divided solid which is in admixture with the finely divided active ingredient. In tablets the active ingredient is mixed with a carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain from about 1 to about 99 weight percent of the active ingredient which is the novel compound of this invention. Suitable solid carriers are magnesium carbonate, magnesium stearate, talc, sugar lactose, pectin, dextrin, starch, gelatin, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, low melting waxes, and cocoa butter.

Sterile liquid form formulations include suspensions, emulsions, syrups and elixirs.

The active ingredient can be dissolved or suspended in a pharmaceutically acceptable carrier, such as sterile water, sterile organic solvent or a mixture of both. The active ingredient can often be dissolved in a suitable organic solvent, for instance aqueous propylene glycol. Other compositions can be made by dispersing the finely divided active ingredient in aqueous starch or sodium carboxymethyl cellulose solution or in a suitable oil.

The following pharmaceutical formulations 1 through 8 are illustrative only and are not intended to limit the scope of the invention in any way. "Active ingredient", refers to a compound according to Formula (III) or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

Formulation 1

Hard gelatin capsules are prepared using the following ingredients:

	Quantity (mg/capsule)
Compound of Example 5	250
Starch, dried	200
Magnesium stearate	10
Total	460 mg

Formulation 2

A tablet is prepared using the ingredients below:

	Quantity (mg/tablet)
Compound of Example 10	250
Cellulose, microcrystalline	400
Silicon dioxide, fumed	10
Stearic acid	5
Total	665 mg

The components are blended and compressed to form tablets each weighing 665 mg

Formulation 3

An aerosol solution is prepared containing the following components:

	Weight
Compound of Example 15	0.25
Ethanol	25.75
Propellant 22 (Chlorodifluoromethane)	74.00
Total	100.00

The active compound is mixed with ethanol and the mixture added to a portion of the propellant 22, cooled to -30°C and transferred to a filling device. The required amount is then fed to a stainless steel container and diluted with the remainder of the propellant. The valve units are then fitted to the container.

Formulation 4

Tablets, each containing 60 mg of active ingredient, are made as follows:

Compound of Example 25	60 mg
Starch	45 mg
Microcrystalline cellulose	35 mg
Polyvinylpyrrolidone (as 10% solution in water)	4 mg
Sodium carboxymethyl starch	4.5 mg
Magnesium stearate	0.5 mg
Talc	1 mg
Total	150 mg

The active ingredient, starch and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The aqueous solution containing polyvinylpyrrolidone is mixed with the resultant powder, and the mixture then is passed through a No. 14 mesh U.S. sieve. The granules so produced are dried at 50°C and passed through a No. 18 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate and talc, previously passed through a No. 60 mesh U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 150 mg.

Formulation 5

Capsules, each containing 80 mg of active ingredient, are made as follows:

Compound of Example 30	80 mg
Starch	59 mg
Microcrystalline cellulose	59 mg
Magnesium stearate	2 mg
Total	200 mg

The active ingredient, cellulose, starch, and magnesium stearate are blended, passed through a No. 45 mesh U.S. sieve, and filled into hard gelatin capsules in 200 mg quantities.

Formulation 6

Suppositories, each containing 225 mg of active ingredient, are made as follows:

Compound of Example 35	225 mg
Saturated fatty acid glycerides	2,000 mg
Total	2,225 mg

The active ingredient is passed through a No. 60 mesh U.S. sieve and suspended in the saturated fatty acid glycerides previously melted using the minimum heat necessary. The mixture is then poured into a suppository mold of nominal 2 g capacity and allowed to cool.

Formulation 7

Suspensions, each containing 50 mg of active ingredient per 5 ml dose, are made as follows:

Compound of Example 40	50 mg
Sodium carboxymethyl cellulose	50 mg
Syrup	1.25 ml
Benzoic acid solution	0.10 ml
Flavor	q.v.
Color	q.v.
Purified water to total	5 ml

The active ingredient is passed through a No. 45 mesh U.S. sieve and mixed with the sodium carboxymethyl cellulose and syrup to form a smooth paste. The benzoic acid solution, flavor and color are diluted with a portion of the water and added, with stirring. Sufficient water is then added to produce the required volume.

Formulation 8

An intravenous formulation may be prepared as follows:

Compound of Example 45	100 mg
Isotonic saline	1,000 ml

The solution of the above ingredients generally is administered intravenously to a subject at a rate of 1 ml per minute.

Assay Example 1

The following chromogenic assay procedure was used to identify and evaluate inhibitors of recombinant human secreted phospholipase A_2. The assay described herein has been adapted for high volume screening using 96 well microtiter plates. A general description of this assay method is found in the article, "Analysis of Human Synovial Fluid Phospholipase A_2 on Short Chain Phosphatidylcholine-Mixed Micelles: Development of a Spectrophotometric Assay Suitable for a Microtiterplate Reader", by Laure J. Reynolds, Lori L. Hughes, and Edward A Dennis, Analytical Biochemistry, 204, pp. 190-197, 1992 (the disclosure of which is incorporated herein by reference):

Reagents:

REACTION BUFFER -

$CaCl_2.2H_2O$ (1.47 g/L)

KCl (7.455 g/L)

Bovine Serum Albumin (fatty acid free) (1 g/L)
(Sigma A-7030, product of Sigma Chemical Co. St. Louis MO, USA)

TRIS HCl (3.94 g/L)
pH 7.5 (adjust with NaOH)

ENZYME BUFFER -
0.05 $NaOAc.3H_2O$, pH 4.5
0.2 NaCl
Adjust pH to 4.5 with acetic acid

DTNB -
5,5'-dithiobis-2-nitrobenzoic acid

RACEMIC DIHEPTANOYL THIO - PC
racemic 1,2-bis(heptanoylthio)-1,2-dideoxy-*sn*-glycero-3-phosphorylcholine
TRITON X-100™ prepare at 6.249 mg/ml in reaction buffer to equal 10uM
TRITON X-100™ is a polyoxy ethylene non-ionic detergent supplied by
Pierce Chemical Company,
3747 N. Meridian Road, Rockford, Illinois 61101.

REACTION MIXTURE -

A measured volume of racemic diheptanoyl thio PC supplied in chloroform at a concentration of 100 mg/ml is taken to dryness and redissolved in 10 millimolar TRITON X-100™ nonionic detergent aqueous solution. Reaction Buffer is added to the solution, then DTNB to give the Reaction Mixture.

The reaction mixture thus obtained contains 1mM diheptanoly thio-PC substrate, 0.29 mm Triton X-100™ detergent, and 0.12 mm DTMB in a buffered aqueous solution at pH 7.5.

Assay Procedure:

1. Add 0.2 ml reaction mixture to all wells;

2. Add 10 ul test compound (or solvent blank) to appropriate wells, mix 20 seconds;

3. Add 50 nanograms of $sPLA_2$ (10 microliters) to appropriate wells;

4. Incubate plate at 40°C for 30 minutes;

5. Read absorbance of wells at 405 nanometers with an automatic plate reader.

All compounds were tested in triplicate. Typically, compounds were tested at a final concentration of 5 ug/ml. Compounds were considered active when they exhibited 40% inhibition or greater compared to uninhibited control reactions when measured at 405 nanometers. Lack of color development at 405 nanometers evidenced inhibition. Compounds initially found to be active were reassayed to confirm their activity and, if sufficiently active, IC_{50} values were determined. Typically, the IC_{50} values (see, Table I, below) were determined by diluting test compound serially two-fold such that the final concentration in the reaction ranged from 45 ug/mL to 0.35 ug/ml. More potent inhibitors required significantly greater dilution. In all cases, % inhibition measured at 405 nanometers generated by enzyme reactions containing inhibitors relative to the uninhibited control reactions was determined. Each sample was titrated in triplicate and result values were averaged for plotting and calculation of IC_{50} values. IC_{50} were determined by plotting log concentration versus inhibition values in the range from 10-90% inhibition.

Compounds of the instant invention were tested in Assay Example 1 and were found to be effective at concentrations of less than 100μM.

Assay Example 2

Method:

Male Hartley strain guinea pigs (500-700g) were killed by cervical dislocation and their heart and lungs removed intact and placed in aerated (95% O_2:5% CO_2) Krebs buffer. Dorsal pleural strips (4x1x25mm) were dissected from intact parenchymal segments (8x4x25mm) cut parallel to the outer edge of the lower lung lobes. Two adjacent pleural strips, obtained from a single lobe and representing a single tissue sample, were tied at either end and independently attached to a metal support rod. One rod was attached to a Grass force-displacement transducer Model FT03C, product of Grass Medical Instruments Co., Quincy, MA, USA). Changes in isometric tension were displayed on a monitor and thermal recorder (product of Modular Instruments, Malvern, PA). All tissues were placed in 10 ml jacketed tissue baths maintained at 37°C. The tissue baths were continuously aerated and contained a modified Krebs solution of the following composition (millimolar) NaCl, 118.2; KCl, 4.6; $CaCl_2 \cdot 2H_2O$, 2.5; $MgSO_4 \cdot 7H_2O$, 1.2; $NaHCO_3$, 24.8; KH_2PO_4, 1.0; and dextrose, 10.0. Pleural strips from the opposite lobes of the lung were used for paired experiments. Preliminary data generated from tension/response curves demonstrated that resting tension of 800mg was optimal. The tissues were allowed to equilibrate for 45 min. as the bath fluid was changed periodically.

Cumulative concentration-response curves:

Initially tissues were challenged 3 times with KCl (40 mM) to test tissue viability and to obtain a consistent response. After recording the maximal response to KCl, the tissues were washed and allowed to return to

baseline before the next challenge. Cumulative concentration-response curves were obtained from pleural strips by increasing the agonist concentration ($sPLA_2$) in the tissue bath by half-log_{10} increments while the previous concentration remained in contact with the tissues (Ref.1, supra.). Agonist concentration was increased after reaching the plateau of the contraction elicited by the preceding concentration. One concentration-response curve was obtained from each tissue. To minimize variability between tissues obtained from different animals, contractile responses were expressed as a percentage of the maximal response obtained with the final KCl challenge. When studying the effects of various drugs on the contractile effects of $sPLA_2$, the compounds and their respective vehicles were added to the tissues 30 minutes prior to starting the $sPLA_2$ concentration-response curves.

Statistical analysis:

Data from different experiments were pooled and presented as a percentage of the maximal KCl responses (mean ± S.E.). To estimate the drug induced rightward shifts in the concentration response curves, the curves were analyzed simultaneously using statistical nonlinear modeling methods similar to those described by Waud (1976), Equation 26, p. 163, (Ref.2). The model includes four parameters: the maximum tissue response which was assumed the same for each curve, the ED_{50} for the control curve, the steepness of the curves, and the pA_2, the concentration of antagonist that requires a two-fold increase in agonist to achieve an equivalent response. The Schild slope was determined to be 1, using statistical nonlinear modeling methods similar to those described by Waud (1976), Equation 27, p. 164 (Ref. 2). The Schild

slope equal to 1 indicates the model is consistent with the assumptions of a competitive antagonist; therefore, the pA2 may be interpreted as the apparent K_B, the dissociation constant of the inhibitor.

To estimate the drug-induced suppression of the maximal responses, $sPLA_2$ responses (10 ug/ml) were determined in the absence and presence of drug, and percent suppression was calculated for each pair of tissues. Representative examples of inhibitory activities are presented in Table 2, below.

Ref. 1 - Van, J.M.: Cumulative dose-response curves. II. Technique for the making of dose-response curves in isolated organs and the evaluation of drug parameters. Arch. Int. Pharmacodyn. Ther., 143: 299-330, 1963.

Ref. 2 - Waud, D.: Analysis of dose-response relationships. in Advances in General and Cellular Pharmacology eds Narahashi, Bianchi 1:145-178, 1976.

Compounds of the instant invention were tested in Assay Example 2 and were found to be effective at concentrations below 20μM.

Assay Example 3

$sPLA_2$ Transgenic Mice Assay

Materials & Methods

The mice utilized in these studies were mature, 6-8 month old, $ZnSO_4$-stimulated, hemizygous line 2608^a transgenic mice (Fox et. al. 1996). Transgenic mice from this line express human $sPLA_2$ in the liver and other tissues and typically achieve levels of human $sPLA_2$ in

their circulation of approximately 173 ± 10 ng/ml when maximally stimulated with $ZnSO_4$ (Fox, *et al.* 1996). The mice were housed under constant humidity and temperature and received food and water ad libitum. Animal room lighting was maintained on a 12-hour light/dark cycle and all experiments were performed at the same time of the day during the early morning light period.

For intravenous testing, compounds or vehicle were administered as an IV bolus via the tail vein in a volume of 0.15 ml. Vehicle consisted of 1-5% dimethylsulfoxide, 1-5% ethanol and 10-30% polyethylene glycol 300 in H_2O; the concentrations of these ingredients were adjusted according to the solubility of the compound. Mice were bled retro-orbitally prior to drug or vehicle administration and 30 minutes, 2 and 4 hours thereafter. Three to six mice were used for each dose. PLA_2 catalytic activity in the serum was assayed with a modified phosphatidylcholine/deoxycholine mixed micelle assay (Fox, *et al.* 1996, Schadlich, *et al.*, 1987) utilizing 3 mM sodium deoxycholate and 1 mM 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine.

For oral testing, compounds were dissolved in 1-5% ethanol/10-30% polyethylene glycol 300 in H_2O or were suspended in 5% dextrose in H_2O and administered by oral gavage. Serum was prepared from retro-orbital blood and assayed for PLA_2 catalytic activity as above.

References

Fox, N., M. Song, J. Schrementi, J. D. Sharp, D. L. White, D. W. Snyder, L. W. Hartley, D. G. Carlson, N. J. Bach, R. D. Dillard, S. E. Draheim, J. L. Bobbitt, L. Fisher and E. D. Mihelich. 1996.

Eur. J. Pharmacol. 308: 195.

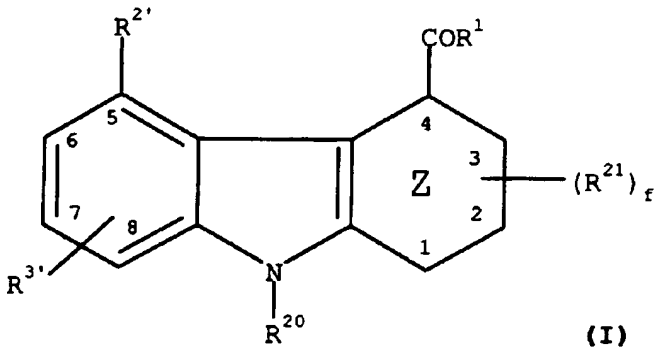
Schadlich, H.R., M. Buchler, and H. G. Beger, 1987, J. Clin. Chem. Clin.
Biochem. 25, 505.

Compounds of the instant invention were tested in Assay Example 3 and were found to be effective.

While the present invention has been illustrated above by certain specific embodiments, it is not intended that these specific examples should limit the scope of the invention as described in the appended claims.

We claim:

1. A compound of the formula (I)



(I)

wherein;

Z is cyclohexenyl, or phenyl,

R^{20} is selected from groups (a), (b) and (c) where;

(a) is -(C_5-C_{20})alkyl, -(C_5-C_{20})alkenyl, -(C_5-C_{20})alkynyl, carbocyclic radicals, or heterocyclic radicals, or

(b) is a member of (a) substituted with one or more independently selected non-interfering substituents; or

(c) is the group -(L)-R^{80}; where, (L)-is a divalent linking group of 1 to 12 atoms selected from carbon, hydrogen, oxygen, nitrogen, and sulfur; wherein the combination of atoms in -(L)- are selected from the group consisting of (i) carbon and hydrogen only, (ii) one sulfur only, (iii) one oxygen only, (iv) one or two nitrogen and hydrogen only, (v) carbon, hydrogen, and one sulfur only, and (vi) an carbon, hydrogen, and oxygen only; and where R^{80} is a group selected from (a) or (b);

R^{21} is a non-interfering substituent where f is 1-3;

R^1 is $-NHNH_2$, $-NH_2$, or $-CONH_2$;

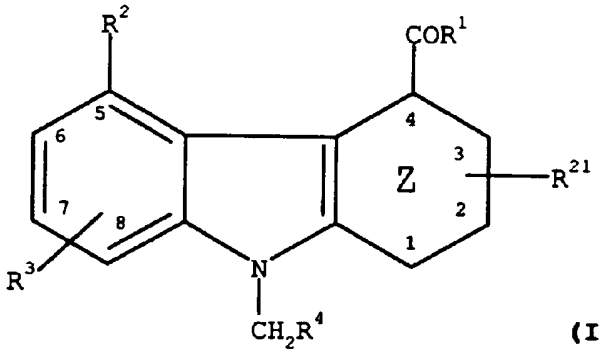
$R^{2'}$ is selected from the group consisting of -OH, and $-O(CH_2)_tR^{5'}$ where

$R^{5'}$ is H, -CN, $-NH_2$, $-CONH_2$, $-CONR^9R^{10}$ $-NHSO_2R^{15}$; $-CONHSO_2R^{15}$, where R^{15} is $-(C_1-C_6)$alkyl or $-CF_3$; phenyl or phenyl substituted with $-CO_2H$ or $-CO_2(C_1-C_4)$alkyl; and $-(L_a)-$(acidic group), wherein $-(L_a)-$ is an acid linker having an acid linker length of 1 to 7 and t is 1-5;

$R^{3'}$ is selected from non-interfering substituent, carbocyclic radicals, carbocyclic radicals substituted with non-interfering substituents, heterocyclic radicals, and heterocyclic radicals substituted with non-interfering substituents;

or a pharmaceutically acceptable racemate, solvate, tautomer, optical isomer, prodrug derivative or salt, thereof.

2. A compound of the formula (II)



(II)

wherein;

Z is cyclohexenyl, or phenyl;

R^{21} is a non-interfering substituent;

R^1 is $-NHNH_2$ or $-NH_2$;

R^2 is selected from the group consisting of -OH and

$-O(CH_2)_mR^5$ where

R^5 is H, $-CO_2H$, $-CONH_2$, $-CO_2(C_1-C_4$ alkyl); $-\overset{O}{\overset{\|}{P}}(R^6R^7)$, where R^6 and R^7 are each independently $-OH$ or $-O(C_1-C_4)$alkyl; $-SO_3H$, $-SO_3$(C1-C4 alkyl), tetrazolyl, $-CN$, $-NH_2$, $-NHSO_2R^{15}$; $-CONHSO_2R^{15}$, where R^{15} is $-(C_1-C_6)$alkyl or $-CF_3$, phenyl or phenyl substituted with $-CO_2H$ or $-CO_2(C_1-C_4)$alkyl where m is 1-3;

R^3 is H, $-O(C_1-C_4)$alkyl, halo, $-(C_1-C_6)$alkyl, phenyl, $-(C_1-C_4)$alkylphenyl; phenyl substituted with $-(C_1-C_6)$alkyl, halo, or $-CF_3$; $-CH_2OSi(C_1-C_6)$alkyl, furyl, thiophenyl, $-(C_1-C_6)$hydroxyalkyl; or $-(CH_2)_nR^8$ where R^8 is H, $-CONH_2$, $-NR^9R^{10}$, $-CN$ or phenyl where R^9 and R^{10} are independently $-(C_1-C_4)$alkyl or -phenyl(C_1-C_4)alkyl and n is 1 to 8;

R^4 is H, $-(C_5-C_{14})$alkyl, $-(C_3-C_{14})$cycloalkyl, pyridyl, phenyl or phenyl substituted with $-(C_1-C_6)$alkyl, halo, $-CF_3$, $-OCF_3$, $-(C_1-C_4)$alkoxy, $-CN$, $-(C_1-C_4)$alkylthio, phenyl(C1-C_4)alkyl, $-(C_1-C_4)$alkylphenyl, phenyl, phenoxy or naphthyl;

or a pharmaceutically acceptable racemate, solvate, tautomer, optical isomer, prodrug derivative or salt, thereof.

3. A compound of formula (II) as claimed in **Claim 2** wherein

R^1 is-NH_2; and

Z is phenyl.

4. A compound as claimed in any one of **Claims 2 or 3**, wherein R^5 is H, NH_2, $-CONH_2$, $-SO_3H$, $-SO_3(C_1-C_4)$ alkyl, tetrazolyl, $-CN$, $-NH_2$, $-NHSO_2R^{15}$; $-CONHSO_2R^{15}$; where R^{15} is (C_1-C_6) alkyl, $-CF_3$, phenyl or phenyl substituted with $-CO_2H$ or $-Co_2(C_1-C_4)$alkyl.

5. A compound of formula (II) as claimed in any one of **Claims 2-4** wherein R^3 is halo, $-(C_1-C_6)$ alkyl, phenyl, $-(C_1-C_4)$alkylphenyl; phenyl substituted with $-(C_1-C_4)$alkyl, halo, or $-CF_3$; $-CH_2OSi(C_1-C_6)$alkyl, furyl, thiophenyl or (C_1-C_6)hydroxy alkyl.

6. A compound of formula (II) as claimed in any one **of Claims 2-5** wherein R^4 is pyridyl, phenyl substituted with (C_5-C_6) alkyl, $-CF_3$, $-OCF_3$, $-CN$, $-(C_1-C_4)$alkylphenyl, phenoxy or naphthyl.

7. A compound of formula (II) as claimed in any one of **Claims 2-6** wherein R^{21} is selected from the group consisting of hydrogen, halo, $-(C_1-C_3)$alkyl, $-(C_3-C_4)$alkyl, $-(C_3-C_4)$cycloalkyl, $-(C_3-C_4)$cycloalkenyl, $-O(C_1-C_2)$alkyl and $-S(C_1-C_2)$alkyl.

8 A compound of formula (II) as claimed in any one of **Claims 2-7** wherein R^4 is hydrogen.

9. A compound of formula (II) as claimed in any one **of Claims 2-8** wherein R^1 is $-NH_2$ and R^2 is $-O(CH_2)_mR^5$ where R^5 is -H, $-CO_2H$ or $-\overset{O}{\overset{\|}{P}}(R^6R^7)$, where R^6 and R^7 are -OH.

10. A compound of formula (II) as claimed in any one of **Claims 2-8** where R^2 is $-O(CH_2)_mR^5$ where R^5 is -H, $-CO_2(C_1-C_4$ alkyl), phenyl or phenyl substituted with $-CO_2H$ or $-CO_2(C_1-C_4$ alkyl).

11. A compound of formula (II) as claimed in any one of **Claims 2-8** wherein R^2 is $-O(CH_2)_mR^5$ where R^5 is $-\overset{O}{\overset{\|}{P}}(R^6R^7)$ and R^6 and R^7 are $-O(C_1-C_4$ alkyl), or when one of R^6 and R^7 is $-O(C_1-C_4$ alkyl), the other is -OH.

12. A compound of formula (II) as claimed in any one of **Claims 2-11** where R^3 is -H, $-O(C_1-C_4$ alkyl) or $-(CH_2)_nR^8$ where n = 2 and R^8 is H or phenyl.

13. A compound of formula (II) as claimed in any one of **Claims 2-11** where R^3 is H, or $-O(C_1-C_4$ alkyl).

14. A compound of formula (II) as claimed in any one of **Claims 2-11** where R^3 is $-(CH_2)_nR^8$ where R^8 is $-NR^9R^{10}$, $-\overset{O}{\overset{\|}{C}}NH_2$ or -CN where R^9 and R^{10} are $-(C_1-C_4)$alkyl.

15. A compound of formula (II) as claimed in any one **of Claims 2-14** where R^4 is phenyl.

16. A compound of formula (II) as claimed in any one of **Claims 2-14** where R^4 is phenyl substituted at the 2- and 6- position of the phenyl ring with $-(C_1-C_4)$alkyl, (C_1-C_4)alkoxy, halo or phenyl.

17. A compound of formula (II) as claimed in any one of **Claims 2-14** where R^4 is phenyl substituted at the 3- or 5-position of the phenyl ring with $-(C_1-C_4)$alkyl, $-(C_1-C_4)$alkoxy, halo or phenyl.

18. A compound of formula (II) as claimed in any one **of Claims 2-14** where R^4 is -(C_6-C_{14})alkyl or -(C_6-C_{14})cycloalkyl.

19. A compound of formula (II) as claimed in any one of **Claims 2-18** where R^5 is H, $-CO_2H$, $-CO_2$(C_1-C_4 alkyl), $-\overset{O}{\overset{\|}{P}}(R^6R^7)$, $-NHSO_2$(C_1-C_6)alkyl, $-CONHSO_2$(C_1-C_6)alkyl, tetrazolyl, phenyl, or phenyl substituted with $-CO_2H$ or $-CO_2$(C_1-C_4 alkyl) where R^6 and R^7 are each independently -OH or -O(C_1-C_4 alkyl) and m is 1-3;

20. A compound of formula (II) as claimed in any one of **Claims 2-19** where R^5 is H, $-CO_2H$, $-CO_2$(C_1-C_4 alkyl), $-\overset{O}{\overset{\|}{P}}(R^6R^7)$, phenyl, or phenyl substituted with $-CO_2H$ or $-CO_2$(C_1-C_4 alkyl) where R^6 and R^7 are each independently -OH or -O(C_1-C_4 alkyl) and m is 1-3.

21. A compound of formula (II) as claimed in any one **of Claims 2-18** where R^5 is H, $-CO_2H$, $-CO_2$(C_1-C_4 alkyl); $-\overset{O}{\overset{\|}{P}}(R^6R^7)$, where R^6 and R^7 are each independently -OH or -O(C_1-C_4)alkyl; $-SO_3H$, $-SO_3$(C_1-C_4 alkyl), tetrazolyl, -CN, $-NH_2$, $-NHSO_2R^{15}$; $-CONHSO_2R^{15}$, where R^{15} is -(C_1-C_6)alkyl or $-CF_3$, phenyl or phenyl substituted with $-CO_2H$ or $-CO_2$(C_1-C_4)alkyl where m is 1-3.

22. A compound of formula (II) as claimed in any one of **Claims 2-21** where Z is cyclohexenyl.

23. A compound of formula (II) as claimed in any one of **Claims 2-21** where Z is phenyl.

24. A compound as claimed in any one of **Claims 2-23** which is selected from the group consisting of;
9-benzyl-5,7-dimethoxy-1,2,3,4-tetrahydrocarbazole-4-carboxylic acid hydrazide;
9-benzyl-5,7-dimethoxy-1,2,3,4-tetrahydrocarbazole-4-carboxamide;
[9-benzyl-4-carbamoyl-7-methoxy-1,2,3,4-tetrahydrocarbazol-5-yl]oxyacetic acid sodium salt;
[9-benzyl-4-carbamoyl-7-methoxycarbazol-5-yl]oxyacetic acid;
methyl [9-benzyl-4-carbamoyl-7-methoxycarbazol-5-yl]oxyacetic acid;
9-benzyl-7-methoxy-5-cyanomethyloxy-1,2,3,4-tetrahydrocarbazole-4-carboxamide;
9-benzyl-7-methoxy-5-(1H-tetrazol-5-yl-methyl)oxy)-1,2,3,4-tetrahydrocarbazole-4-carboxamide;
{9-[(phenyl)methyl]-5-carbamoyl-2-methyl-carbazol-4-yl}oxyacetic acid;
{9-[(3-fluorophenyl)methyl]-5-carbamoyl-2-methyl-carbazol-4-yl}oxyacetic acid;
{9-[(3-methylphenyl)methyl]-5-carbamoyl-2-methyl-carbazol-4-yl}oxyacetic acid;
{9-[(phenyl)methyl]-5-carbamoyl-2-(4-trifluoromethylphenyl)-carbazol-4-yl}oxyacetic acid;
9-benzyl-5-(2-methanesulfonamido)ethyloxy-7-methoxy-1,2,3,4-tetrahydrocarbazole-4-carboxamide;
9-benzyl-4-(2-methanesulfonamido)ethyloxy-2-methoxycarbazole-5-carboxamide;

9-benzyl-4-(2-trifluoromethanesulfonamido)ethyloxy-2-methoxycarbazole-5-carboxamide;

9-benzyl-5-methanesulfonamidoylmethyloxy-7-methoxy-1,2,3,4-tetrahydrocarbazole-4-carboxamide;

9-benzyl-4-methanesulfonamidoylmethyloxy-carbazole-5-carboxamide;

[5-carbamoyl-2-pentyl-9-(phenylmethyl)carbazol-4-yl]oxyacetic acid;

[5-carbamoyl-2-(1-methylethyl)-9-(phenylmethyl)carbazol-4-yl]oxyacetic acid;

[5-carbamoyl-9-(phenylmethyl)-2-[(tri(-1-methylethyl)silyl)oxymethyl]carbazol-4-yl]oxyacetic acid;

[5-carbamoyl-2-phenyl-9-(phenylmethyl)carbazol-4-yl]oxyacetic acid[5-carbamoyl-2-(4-chlorophenyl)-9-(phenylmethyl)carbazol-4-yl]oxyacetic acid;

[5-carbamoyl-2-(2-furyl)-9-(phenylmethyl)carbazol-4-yl]oxyacetic acid;

[5-carbamoyl-9-(phenylmethyl)-2-[(tri(-1-methylethyl)silyl)oxymethyl]carbazol-4-yl]oxyacetic acid, lithium salt;

{9-[(2-Fluorophenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid;

{9-[(2-trifluoromethylphenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid;

{9-[(2-benzylphenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid;

{9-[(1-naphthyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid;

{9-[(2-cyanophenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid;

{9-[(3-cyanophenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid;

{9-[(3,5-dimethylphenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid;

{9-[(3-iodophenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid;

{9-[(2-Chlorophenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid;

{9-[(2,3-difluorophenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid;

{9-[(2,6-difluorophenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid;

{9-[(2,6-dichlorophenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid;

{9-[(2-biphenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid;

{9-[(2-Biphenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid;

{9-[(2-Biphenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid;

[9-Benzyl-4-carbamoyl-1,2,3,4-tetrahydrocarbaole-5-yl]oxyacetic acid;

{9-[(2-Pyridyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid;

{9-[(3-Pyridyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid;

[9-benzyl-4-carbamoyl-8-methyl-1,2,3,4-tetrahydrocarbazol-5-yl]oxyacetic acid;

[9-benzyl-5-carbamoyl-1-methylcarbazol-4-yl]oxyacetic acid;

[9-benzyl-4-carbamoyl-8-fluoro-1,2,3,4-tetrahydrocarbazol-5-yl]oxyacetic acid;

[9-benzyl-4-carbamoyl-8-chloro-1,2,3,4-tetrahydrocarbazol-5-yl]oxyacetic acid;

5-carbamoyl-9-(phenylmethyl)-2-[[(propen-3-yl)oxy]methyl]carbazol-4-yl]oxyacetic acid;

[5-carbamoyl-9-(phenylmethyl)-2-[(propyloxy)methyl]carbazol-4-yl]oxyacetic acid;

9-benzyl-7-methoxy-5-((carboxamidomethyl)oxy)-1,2,3,4-tetrahydrocarbazole-4-carboxamide;

9-benzyl-7-methoxy-5-cyanomethyloxy-carbazole-4-carboxamide;

9-benzyl-7-methoxy-5-((1H-tetrazol-5-yl-methyl)oxy)-carbazole-4-carboxamide;

9-benzyl-7-methoxy-5-((carboxamidomethyl)oxy)-carbazole-4-carboxamide; and

[9-Benzyl-4-carbamoyl-1,2,3,4-tetrahydrocarbaole-5-yl]oxyacetic acid

or a pharmaceutically acceptable racemate, solvate, tautomer, optical isomer, prodrug derivative or salt, thereof.

25. A compound of any one of **Claims 2-23** which is selected from the group consisting of;

{9-[(phenyl)methyl]-5-carbamoyl-2-methyl-carbazol-4-yl}oxyacetic acid;

{9-[(3-fluorophenyl)methyl]-5-carbamoyl-2-methyl-carbazol-4-yl}oxyacetic acid;

{9-[(3-methylphenyl)methyl]-5-carbamoyl-2-methyl-carbazol-4-yl}oxyacetic acid;

{9-[(phenyl)methyl]-5-carbamoyl-2-(4-trifluoromethylphenyl)-carbazol-4-yl}oxyacetic acid;

9-benzyl-5-(2-methanesulfonamido)ethyloxy-7-methoxy-1,2,3,4-tetrahydrocarbazole-4-carboxamide;

9-benzyl-4-(2-methanesulfonamido)ethyloxy-2-methoxycarbazole-5-carboxamide;

9-benzyl-4-(2-trifluoromethanesulfonamido)ethyloxy-2-methoxycarbazole-5-carboxamide;

9-benzyl-5-methanesulfonamidoylmethyloxy-7-methoxy-1,2,3,4-tetrahydrocarbazole-4-carboxamide;

9-benzyl-4-methanesulfonamidoylmethyloxy-carbazole-5-carboxamide;

[5-carbamoyl-2-pentyl-9-(phenylmethyl)carbazol-4-yl]oxyacetic acid;

[5-carbamoyl-2-(1-methylethyl)-9-(phenylmethyl)carbazol-4-yl]oxyacetic acid;

[5-carbamoyl-9-(phenylmethyl)-2-[(tri(-1-methylethyl)silyl)oxymethyl]carbazol-4-yl]oxyacetic acid;

[5-carbamoyl-2-phenyl-9-(phenylmethyl)carbazol-4-yl]oxyacetic acid[5-carbamoyl-2-(4-chlorophenyl)-9-(phenylmethyl)carbazol-4-yl]oxyacetic acid;

[5-carbamoyl-2-(2-furyl)-9-(phenylmethyl)carbazol-4-yl]oxyacetic acid;

[5-carbamoyl-9-(phenylmethyl)-2-[(tri(-1-methylethyl)silyl)oxymethyl]carbazol-4-yl]oxyacetic acid, lithium salt;

{9-[(phenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid;

{9-[(3-fluorophenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid;

{9-[(3-phenoxyphenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid;

{9-[(2-Fluorophenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid;

{9-[(2-trifluoromethylphenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid;

{9-[(2-benzylphenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid;

{9-[(3-trifluoromethylphenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid;

{9-[(1-naphthyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid;

{9-[(2-cyanophenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid;

{9-[(3-cyanophenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid;

{9-[(2-methylphenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid;

{9-[(3-methylphenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid;

{9-[(3,5-dimethylphenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid;

{9-[(3-iodophenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid;

{9-[(2-Chlorophenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid;

{9-[(2,3-difluorophenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid;

{9-[(2,6-difluorophenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid;

{9-[(2,6-dichlorophenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid;

{9-[(3-trifluoromethoxyphenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid;

{9-[(2-biphenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid;

{9-[(2-Biphenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid;

the {9-[(2-Biphenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid;

[9-Benzyl-4-carbamoyl-1,2,3,4-tetrahydrocarbaole-5-yl]oxyacetic acid;

{9-[(2-Pyridyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid;

{9-[(3-Pyridyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid;

[9-benzyl-4-carbamoyl-8-methyl-1,2,3,4-tetrahydrocarbazol-5-yl]oxyacetic acid;

[9-benzyl-5-carbamoyl-1-methylcarbazol-4-yl]oxyacetic acid;
[9-benzyl-4-carbamoyl-8-fluoro-1,2,3,4-tetrahydrocarbazol-5-yl]oxyacetic acid;
[9-benzyl-5-carbamoyl-1-fluorocarbazol-4-yl]oxyacetic acid;
[9-benzyl-4-carbamoyl-8-chloro-1,2,3,4-tetrahydrocarbazol-5-yl]oxyacetic acid;
[9-benzyl-5-carbamoyl-1-chlorocarbazol-4-yl]oxyacetic acid;
[9-[(Cyclohexyl)methyl]-5-carbamoylcarbazol-4-yl]oxyacetic acid;
[9-[(Cyclopentyl)methyl]-5-carbamoylcarbazol-4-yl]oxyacetic acid;
5-carbamoyl-9-(phenylmethyl)-2-[[(propen-3-yl)oxy]methyl]carbazol-4-yl]oxyacetic acid;
[5-carbamoyl-9-(phenylmethyl)-2-[(propyloxy)methyl]carbazol-4-yl]oxyacetic acid;
9-benzyl-7-methoxy-5-((carboxamidomethyl)oxy)-1,2,3,4-tetrahydrocarbazole-4-carboxamide;
9-benzyl-7-methoxy-5-cyanomethyloxy-carbazole-4-carboxamide;
9-benzyl-7-methoxy-5-((1H-tetrazol-5-yl-methyl)oxy)-carbazole-4-carboxamide;
9-benzyl-7-methoxy-5-((carboxamidomethyl)oxy)-carbazole-4-carboxamide; and
[9-Benzyl-4-carbamoyl-1,2,3,4-tetrahydrocarbaole-5-yl]oxyacetic acid

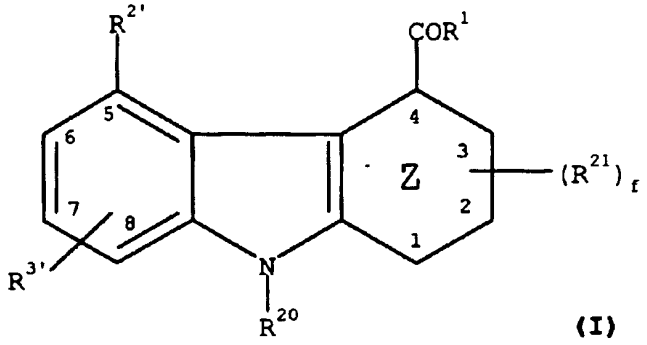
or a pharmaceutically acceptable racemate, solvate, tautomer, optical isomer, prodrug derivative or salt, thereof.

26. A compound as claimed in any one of **Claims 1-23** wherein the prodrug derivative is a methyl, ethyl, propyl, isopropyl, butyl, morpholinoethyl or diethylglycolamide ester.

27. A pharmaceutical formulation comprising a compound of formula I as claimed in any one of **Claims 1-23** together with a pharmaceutically acceptable carrier or diluent therefor.

28. A pharmaceutical formulation adapted for the treatment of a condition associated with inhibiting $sPLA_2$, containing a compound of formula I as claimed in any one of **Claims 1-23** together with a pharmaceutically acceptable carrier or diluent therefor.

29. A method of selectively inhibiting $sPLA_2$ in a mammal in need of such treatment comprising administering to said mammal a therapeutically effective amount of a compound of formula (I)



(I)

wherein;

Z is cyclohexenyl, or phenyl,

R^{20} is selected from groups (a), (b) and (c) where;

(a) is -(C5-C20)alkyl, -(C5-C20)alkenyl, -(C5-C20)alkynyl, carbocyclic radicals, or heterocyclic radicals, or

(b) is a member of (a) substituted with one or more independently selected non-interfering substituents; or

(c) is the group $-(L)-R^{80}$; where, (L)-is a divalent linking group of 1 to 12 atoms selected from carbon, hydrogen, oxygen, nitrogen, and sulfur; wherein the combination of atoms in -(L)- are selected from the group consisting of (i) carbon and hydrogen only, (ii) one sulfur only, (iii) one oxygen only, (iv) one or two nitrogen and hydrogen only, (v) carbon, hydrogen, and one sulfur only, and (vi) an carbon, hydrogen, and oxygen only; and where R^{80} is a group selected from (a) or (b);

R^{21} is a non-interfering substituent where f is 1-3;

R^1 is $-NHNH_2$, $-NH_2$, or $-CONH_2$;

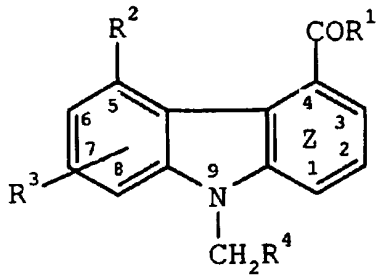
$R^{2'}$ is selected from the group consisting of -OH, and $-O(CH_2)_tR^{5'}$ where

$R^{5'}$ is H, -CN, $-NH_2$, $-CONH_2$, $-CONR^9R^{10}$ $-NHSO_2R^{15}$; $-CONHSO_2R^{15}$, where R^{15} is $-(C_1-C_6)$alkyl or $-CF_3$; phenyl or phenyl substituted with $-CO_2H$ or $-CO_2(C_1-C_4)$alkyl; and $-(L_a)-$(acidic group), wherein $-(L_a)-$ is an acid linker having an acid linker length of 1 to 7 and t is 1-5;

$R^{3'}$ is selected from non-interfering substituent, carbocyclic radicals, carbocyclic radicals substituted with non-interfering substituents, heterocyclic radicals, and heterocyclic radicals substituted with non-interfering substituents;

or a pharmaceutically acceptable racemate, solvate, tautomer, optical isomer, prodrug derivative or salt, thereof.

30. A method of selectively inhibiting $sPLA_2$ in a mammal in need of such treatment comprising administering to said mammal a therapeutically effective amount of a compound of formula (II)



(II)

wherein;

R^1 is $-NHNH_2$, or $-NH_2$;

R^2 is selected from the group consisting of -OH and $-O(CH_2)_mR^5$ where

R^5 is H, $-CO_2H$, $-CONH_2$, $-CO_2(C_1-C_4$ alkyl); $-\overset{O}{\overset{\|}{P}}(R^6R^7)$, where R^6 and R^7 are each independently -OH or $-O(C_1-C_4)$alkyl; $-SO_3H$, $-SO_3$(C1-C4 alkyl), tetrazolyl, -CN, $-NH_2$, $-NHSO_2R^{15}$; $-CONHSO_2R^{15}$, where R^{15} is $-(C_1-C_6)$alkyl or $-CF_3$, phenyl or phenyl substituted with $-CO_2H$ or $-CO_2(C_1-C_4)$alkyl where m is 1-3;

R^3 is H, $-O(C_1-C_4)$alkyl, halo, $-(C_1-C_6)$alkyl, phenyl, $-(C_1-C_4)$alkylphenyl; phenyl substituted with $-(C_1-C_6)$alkyl, halo, or $-CF_3$; $-CH_2OSi(C_1-C_6)$alkyl, furyl, thiophenyl, $-(C_1-C_6)$hydroxyalkyl; or $-(CH_2)_nR^8$ where R^8 is H, $-CONH_2$, $-NR^9R^{10}$, -CN or phenyl where R^9 and R^{10} are independently $-(C_1-C_4)$alkyl or -phenyl(C_1-C_4)alkyl and n is 1 to 8;

R^4 is H, $-(C_5-C_{14})$alkyl, $-(C_3-C_{14})$cycloalkyl, pyridyl, phenyl or phenyl substituted with $-(C_1-C_6)$alkyl, halo, $-CF_3$, $-OCF_3$, $-(C_1-C_4)$alkoxy, -CN, $-(C_1-C_4)$alkylthio, phenyl(C1-C_4)alkyl, $-(C_1-C_4)$alkylphenyl, phenyl, phenoxy or naphthyl;

Z is cyclohexenyl, or phenyl;

or a pharmaceutically acceptable racemate, solvate, tautomer, optical isomer, prodrug derivative or salt, thereof.

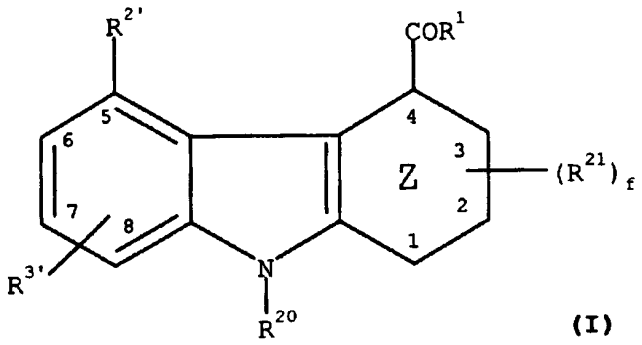
31. A method as claimed in any one of **Claims 30 or 31** wherein the mammal is a human.

32. A method of alleviating the pathological effects of $sPLA_2$ related diseases which comprises administering to a mammal in need of such treatment a compound of formula I as claimed in any one of **Claims 1-23** in an amount sufficient to inhibit $sPLA_2$ mediated release of fatty acid and to thereby inhibit or prevent the arachidonic acid cascade and its deleterious products.

33. The use of a compound as claimed in any one of **Claims 1-23** for the manufacture of a medicament for alleviating the pathological effects of $sPLA_2$ related diseases which comprises administering to a mammal in need of such treatment a compound of formula I.

34. A method of inhibiting $sPLA_2$ which comprises contacting the $sPLA_2$ with a compound as claimed in any one of **Claims 1-23.**

35. A method of treating sepsis, septic shock, rheumatoid arthritis, osteoarthritis, stroke, apoptosis, asthma, chronic bronchitis, acute bronchitis, cystic fibrosis, inflammatory bowel disease, or pancreatitis which comprises administering to a subject in need of such treatment, a therapeutically effective amount of a compound of formula I



(I)

wherein;

Z is cyclohexenyl, or phenyl,

R^{20} is selected from groups (a), (b) and (c) where;

(a) is -(C5-C20)alkyl, -(C5-C20)alkenyl, -(C5-C20)alkynyl, carbocyclic radicals, or heterocyclic radicals, or

(b) is a member of (a) substituted with one or more independently selected non-interfering substituents; or

(c) is the group -(L)-R^{80}; where, (L)-is a divalent linking group of 1 to 12 atoms selected from carbon, hydrogen, oxygen, nitrogen, and sulfur; wherein the combination of atoms in -(L)- are selected from the group consisting of (i) carbon and hydrogen only, (ii) one sulfur only, (iii) one oxygen only, (iv) one or two nitrogen and hydrogen only, (v) carbon, hydrogen, and one sulfur only, and (vi) an carbon, hydrogen, and oxygen only; and where R^{80} is a group selected from (a) or (b);

R^{21} is a non-interfering substituent where f is 1-3;

R^1 is $-NHNH_2$, $-NH_2$, or $-CONH_2$;

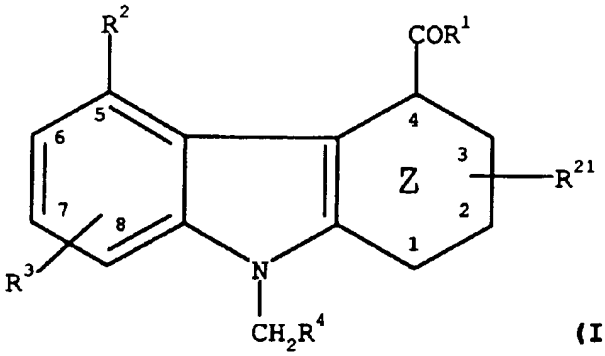
$R^{2'}$ is selected from the group consisting of -OH, and $-O(CH_2)_tR^{5'}$ where

$R^{5'}$ is H, -CN, $-NH_2$, $-CONH_2$, $-CONR^9R^{10}$ $-NHSO_2R^{15}$; $-CONHSO_2R^{15}$, where R^{15} is $-(C_1-C_6)$alkyl or $-CF_3$; phenyl or phenyl substituted with $-CO_2H$ or $-CO_2(C_1-C_4)$alkyl; and $-(L_a)-$(acidic group), wherein $-(L_a)-$ is an acid linker having an acid linker length of 1 to 7 and t is 1-5;

$R^{3'}$ is selected from non-interfering substituent, carbocyclic radicals, carbocyclic radicals substituted with non-interfering substituents, heterocyclic radicals, and heterocyclic radicals substituted with non-interfering substituents;

or a pharmaceutically acceptable racemate, solvate, tautomer, optical isomer, prodrug derivative or salt, thereof.

36. A method of treating sepsis, septic shock, rheumatoid arthritis, osteoarthritis, stroke, apoptosis, asthma, chronic bronchitis, acute bronchitis, cystic fibrosis, inflammatory bowel disease, or pancreatitis which comprises administering to a subject in need of such treatment, a therapeutically effective amount of a compound of formula II



(II)

wherein;

Z is cyclohexenyl, or phenyl,

R^{21} is a non-interfering substituent;

R^1 is $-NHNH_2$ or $-NH_2$;

R^2 is selected from the group consisting of -OH and $-O(CH_2)_mR^5$ where

R^5 is H, $-CO_2H$, $-CONH_2$, $-CO_2(C_1-C_4$ alkyl); $-\overset{O}{\overset{\|}{P}}(R^6R^7)$, where R^6 and R^7 are each independently -OH or $-O(C_1-C_4)$alkyl; $-SO_3H$, $-SO_3$(C1-C4 alkyl), tetrazolyl, -CN, $-NH_2$, $-NHSO_2R^{15}$; $-CONHSO_2R^{15}$, where R^{15} is $-(C_1-C_6)$alkyl or $-CF_3$, phenyl or phenyl substituted with $-CO_2H$ or $-CO_2(C_1-C_4)$alkyl where m is 1-3;

R^3 is H, $-O(C_1-C_4)$alkyl, halo, $-(C_1-C_6)$alkyl, phenyl, $-(C_1-C_4)$alkylphenyl; phenyl substituted with $-(C_1-C_6)$alkyl, halo, or $-CF_3$; $-CH_2OSi(C_1-C_6)$alkyl, furyl, thiophenyl, $-(C_1-C_6)$hydroxyalkyl; or $-(CH_2)_nR^8$ where R^8 is H, $-CONH_2$, $-NR^9R^{10}$, -CN or phenyl where R^9 and R^{10} are independently $-(C_1-C_4)$alkyl or -phenyl(C_1-C_4)alkyl and n is 1 to 8;

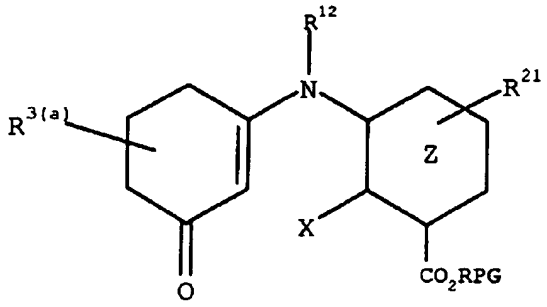
R^4 is H, $-(C_5-C_{14})$alkyl, $-(C_3-C_{14})$cycloalkyl, pyridyl, phenyl or phenyl substituted with $-(C_1-C_6)$alkyl, halo, $-CF_3$, $-OCF_3$, $-(C_1-C_4)$alkoxy, -CN, $-(C_1-C_4)$alkylthio, phenyl(C1-C_4)alkyl, $-(C_1-C_4)$alkylphenyl, phenyl, phenoxy or naphthyl;

or a pharmaceutically acceptable racemate, solvate, tautomer, optical isomer, prodrug derivative or salt, thereof.

37. A method as claimed in any one of **Claims 30-31** of alleviating the pathological effects of sepsis, septic shock, adult respiratory distress syndrome, pancreatitis, trauma-induced shock, bronchial asthma, allergic rhinitis, rheumatoid arthritis, cystic fibrosis, stroke, acute bronchitis, chronic bronchitis, acute bronchiolitis, chronic bronchiolitis, osteoarthritis, gout, spondylarthropathris, ankylosing spondylitis, Reiter's syndrome, psoriatic arthropathy, enterapathric spondylitis, Juvenile arthropathy or juvenile ankylosing spondylitis, Reactive arthropathy,

infectious or post-infectious arthritis, gonoccocal arthritis, Tuberculous arthritis, viral arthritis, fungal arthritis, syphilitic arthritis, Lyme disease, arthritis associated with "vasculitic syndromes", polyarteritis nodosa, hypersensitivity vasculitis, Luegenec's granulomatosis, polymyalgin rheumatica, joint cell arteritis, calcium crystal deposition arthropathris, pseudo gout, non-articular rheumatism, bursitis, tenosynomitis, epicondylitis (tennis elbow), carpal tunnel syndrome, repetitive use injury (typing), miscellaneous forms of arthritis, neuropathic joint disease (charco and joint), hemarthrosis (hemarthrosic), Henoch-Schonlein Purpura, hypertrophic osteoarthropathy, multicentric reticulohistiocytosis, arthritis associated with certain diseases, surcoilosis, hemochromatosis, sickle cell disease and other hemoglobinopathries, hyperlipoproteineimia, hypogammaglobulinemia, hyperparathyroidism, acromegaly, familial Mediterranean fever, Behat's Disease, systemic lupus erythrematosis, or relapsing polychondritis; and related diseases which comprises administering to a mammal in need of such treatment a therapeutically effective amount of a compound of formula I.

38. A compound of the formula



(III)

wherein

PG is an acid protecting group

R^{21} is a non-interfering substituent;

R^{12} is H or CH_2R^4 where

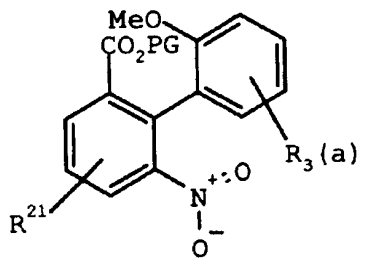
R^4 is H, -(C_5-C_{14})alkyl, -(C_3-C_{14})cycloalkyl, pyridyl, phenyl or phenyl substituted with from 1-5 substituents selected from the group consisting of -(C_1-C_6)alkyl, halo, $-CF_3$, $-OCF_3$, -(C_1-C_4)alkoxy, -CN, -(C_1-C_4)alkylthio, phenyl(C1-C_4)alkyl, -(C_1-C_4)alkylphenyl, phenyl, phenoxy, $-OR^9$; where R^9 and R^{10} are independently hydrogen, $-CF_3$, phenyl, -(C_1-C_4)alkyl, -(C_1-C_4)alkylphenyl or -phenyl(C_1-C_4)alkyl; tetrazole; tetrazole substituted with -(C_1-C_4)alkyl or -(C_1-C_4)alkylphenyl: or naphthyl;

R^3(a) is H, -O(C_1-C_4)alkyl, halo, -(C_1-C_6)alkyl, phenyl, -(C_1-C_4)alkylphenyl; phenyl substituted with -(C_1-C_6)alkyl, halo or $-CF_3$; $-CH_2OSi$(C_1-C_6)alkyl, furyl, thiophenyl, -(C_1-C_6)hydroxyalkyl, -(C_1-C_6)alkoxy(C_1-C_6)alkyl, -(C_1-C_6)alkoxy(C_1-C_6)alkenyl; or $-(CH_2)_nR^8$ where R^8 is H, $-NR^9R^{10}$, -CN or phenyl where R^9 and R^{10} are independently hydrogen, $-CF_3$, phenyl, -(C_1-C_4)alkyl, -(C_1-C_4)alkylphenyl or -phenyl(C_1-C_4)alkyl and n is 1 to 8:

Z is cyclohexenyl or phenyl; and

X is halo.

39. A compound of formula

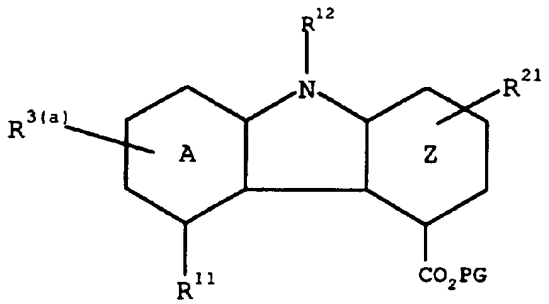


XVIII

where PG is an acid protecting group;

R^{21} is a non-interfering substituent; and
R^3(a) is H, -O(C_1-C_4)alkyl, halo, -(C_1-C_6)alkyl, phenyl, -(C_1-C_4)alkylphenyl; phenyl substituted with -(C_1-C_6)alkyl, halo or -CF_3; -CH_2OSi(C_1-C_6)alkyl, furyl, thiophenyl, -(C_1-C_6)hydroxyalkyl, -(C_1-C_6)alkoxy(C_1-C_6)alkyl, -(C_1-C_6)alkoxy(C_1-C_6)alkenyl; or -$(CH_2)_n R^8$ where R^8 is H, -NR^9R^{10}, -CN or phenyl where R^9 and R^{10} are independently hydrogen, -CF_3, phenyl, -(C_1-C_4)alkyl, -(C_1-C_4)alkylphenyl or -phenyl(C_1-C_4)alkyl and n is 1 to 8.

40. A compound of the formula (IV)



(IV)

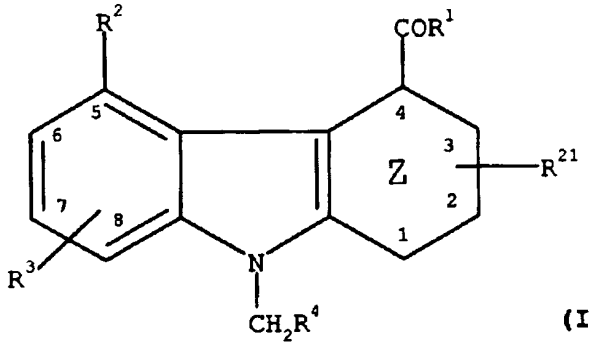
PG is an acid protecting group
R^{21} is a non-interfering substituent
R^{12} is H or CH_2R^4 where
R^4 is H, -(C_5-C_{14})alkyl, -(C_3-C_{14})cycloalkyl, pyridyl, phenyl or phenyl substituted with from 1-5 substituents selected from the group consisting of -(C_1-C_6)alkyl, halo, -CF_3, -OCF_3, -(C_1-C_4)alkoxy, -CN, -(C_1-C_4)alkylthio, phenyl(C1-C_4)alkyl, -(C_1-C_4)alkylphenyl, phenyl, phenoxy, -OR^9; where R^9 and R^{10} are independently hydrogen, -CF_3, phenyl, -(C_1-C_4)alkyl, -(C_1-C_4)alkylphenyl or -phenyl(C_1-C_4)alkyl; tetrazole; tetrazole substituted with -(C_1-C_4)alkyl or -(C_1-C_4)alkylphenyl: or naphthyl;
R^3(a) is H, -O(C_1-C_4)alkyl, halo, -(C_1-C_6)alkyl, phenyl, -(C_1-C_4)alkylphenyl; phenyl substituted with -(C_1-C_6)alkyl,

halo or $-CF_3$; $-CH_2OSi(C_1-C_6)$alkyl, furyl, thiophenyl, $-(C_1-C_6)$hydroxyalkyl, $-(C_1-C_6)$alkoxy(C_1-C_6)alkyl, $-(C_1-C_6)$alkoxy(C_1-C_6)alkenyl; or $-(CH_2)_nR^8$ where R^8 is H, $-NR^9R^{10}$, -CN or phenyl where R^9 and R^{10} are independently hydrogen, $-CF_3$, phenyl, $-(C_1-C_4)$alkyl, $-(C_1-C_4)$alkylphenyl or -phenyl(C_1-C_4)alkyl and n is 1 to 8;

R^{11} is -OH, =O, $-O(C_1-C4)$alkyl or $-O(CH_2)R^{15}$, where R^{15} is $-CO_2R^{16}$, $-SO_3R^{16}$, $P(O)(OR^{16})_2$, or $-P(O)(OR^{16})H$, where R^{16} is an acid protecting group ; and

A and Z are each independently phenyl or cyclohexenyl provided that A and Z cannot both be phenyl.

41. A process of preparing compounds of formula II



(II)

wherein;

Z is cyclohexenyl, or phenyl,

R^{21} is a non-interfering substituent;

R^1 is $-NHNH_2$ or $-NH_2$;

R^2 is selected from the group consisting of -OH, $-O(CH_2)_mR^5$ where

R^5 is H, $-CO_2H$, $-CO_2(C_1-C_4$ alkyl); $-\overset{O}{\overset{\|}{P}}(R^6R^7)$, where R^6 and R^7 are each independently -OH or $-O(C_1-C_4)$alkyl; $-SO_3H$, $-SO_3$(C1-C4 alkyl), tetrazolyl, -CN, $-NH_2$, $-NHSO_2R^{15}$; $-CONHSO_2R^{15}$, where R^{15} is $-(C_1-C_6)$alkyl or $-CF_3$, phenyl

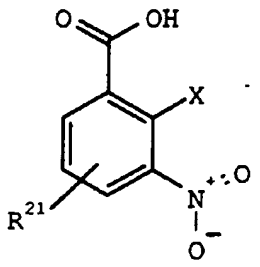
or phenyl substituted with $-CO_2H$ or $-CO_2(C_1-C_4)$alkyl where m is 1-3;

R^3 is H, $-O(C_1-C_4)$alkyl, halo, $-(C_1-C_6)$alkyl, phenyl, $-(C_1-C_4)$alkylphenyl; phenyl substituted with $-(C_1-C_6)$alkyl, halo, or $-CF_3$; $-CH_2OSi(C_1-C_6)$alkyl, furyl, thiophenyl, $-(C_1-C_6)$hydroxyalkyl; or $-(CH_2)_nR^8$ where R^8 is H, $-CONH_2$, $-NR^9R^{10}$, -CN or phenyl where R^9 and R^{10} are independently $-(C_1-C_4)$alkyl or -phenyl(C_1-C_4)alkyl and n is 1 to 8;

R^4 is H, $-(C_5-C_{14})$alkyl, $-(C_3-C_{14})$cycloalkyl, pyridyl, phenyl or phenyl substituted with $-(C_1-C_6)$alkyl, halo, $-CF_3$, $-OCF_3$, $-(C_1-C_4)$alkoxy, -CN, $-(C_1-C_4)$alkylthio, phenyl(C1-C_4)alkyl, $-(C_1-C_4)$alkylphenyl, phenyl, phenoxy or naphthyl;

or a pharmaceutically acceptable racemate, solvate, tautomer, optical isomer, prodrug derivative or salt, thereof;

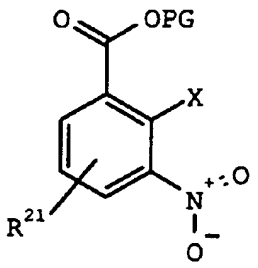
a) esterifying a compound of formula **XVI**



(XVI)

where X is halo;

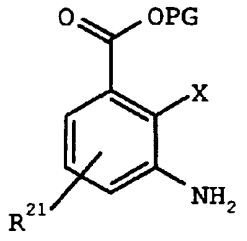
to form a compound of formula **XV**



(XV)

;

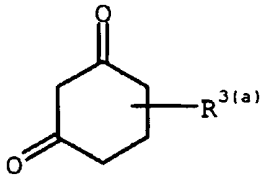
b) reducing a compound of formula **XV** to form a compound of formula **XIV**



(XIV) ;

where PG is an acid protecting group

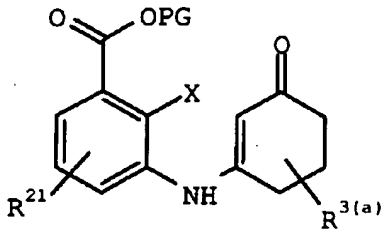
c) condensing a compound of formula **XIV** with a compound of formula **XIII**



(XIII)

where R^3(a) is H, -O(C_1-C_4)alkyl, halo, -(C_1-C_6)alkyl, phenyl, -(C_1-C_4)alkylphenyl; phenyl substituted with -(C_1-C_6)alkyl, halo or $-CF_3$; $-CH_2OSi(C_1$-$C_6)$alkyl, furyl, thiophenyl, -(C_1-C_6)hydroxyalkyl; or $-(CH_2)_nR^8$ where R^8 is H, $-NR^9R^{10}$, -CN or phenyl where R^9 and R^{10} are independently -(C_1-C_4)alkyl or -phenyl(C_1-C_4)alkyl and n is 1 to 8;

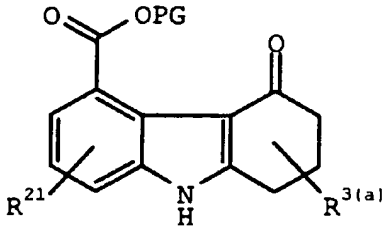
to form a compound of formula **XII**



(XII)

;

d) cyclizing a compound of formula **XII** to form a compound of formula **VI**

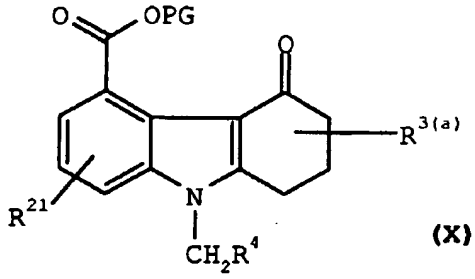


(XI)

;

e) alkylating a compound of formula **XI**

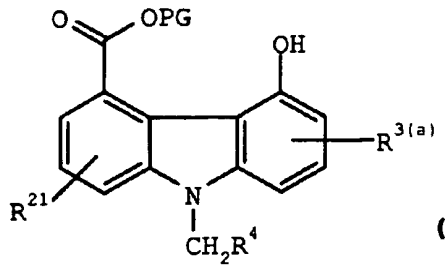
with an alkylating agent of the formula XCH_2R^4, where X is halo to form a compound of formula **X**



(X)

;

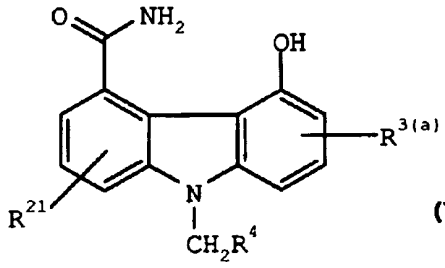
f) dehydrogenating a compound of formula **X** to form a compound of formula **IX**



(IX)

;

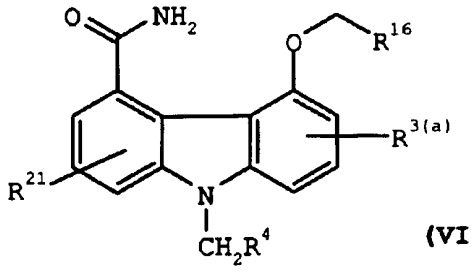
g) aminating a compound of formula **IX** to form a compound of formula **VIII**



(VIII)

;

h) alkylating a compound of formula **VIII** with an alkylating agent of formula XCH_2R^{15} where X is halo and R^{15} is $-CO_2R^{16}$, $-SO_3R^{16}$, $-P(O)(OR^{16})_2$, or $-P(O)(OR^{16})H$, where R^{16} is an acid protecting group to form a compound of formula **VII**

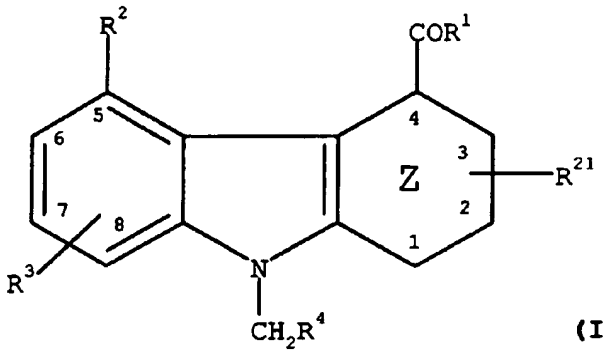


(VII)

;

i) optionally hydrolyzing a compound of formula **VII** to form a compound of formula **I** and optionally salifying a compound of formula I.

42. A process for preparing compounds of formula (II),



(II)

wherein;

Z is cyclohexenyl, or phenyl,

R^{21} is a non-interfering substituent;

R^1 is $-NHNH_2$ or $-NH_2$;

R^2 is selected from the group consisting of -OH and $-O(CH_2)_mR^5$ where

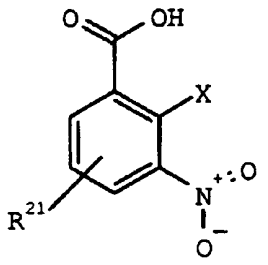
R^5 is H, $-CO_2H$, $-CONH_2$, $-CO_2(C_1-C_4$ alkyl); $-\overset{O}{\overset{\|}{P}}(R^6R^7)$, where R^6 and R^7 are each independently -OH or $-O(C_1-C_4)$alkyl; $-SO_3H$, $-SO_3$(C1-C4 alkyl), tetrazolyl, -CN, $-NH_2$, $-NHSO_2R^{15}$; $-CONHSO_2R^{15}$, where R^{15} is $-(C_1-C_6)$alkyl or $-CF_3$, phenyl or phenyl substituted with $-CO_2H$ or $-CO_2(C_1-C_4)$alkyl where m is 1-3;

R^3 is H, $-O(C_1-C_4)$alkyl, halo, $-(C_1-C_6)$alkyl, phenyl, $-(C_1-C_4)$alkylphenyl; phenyl substituted with $-(C_1-C_6)$alkyl, halo, or $-CF_3$; $-CH_2OSi(C_1-C_6)$alkyl, furyl, thiophenyl, $-(C_1-C_6)$hydroxyalkyl; or $-(CH_2)_nR^8$ where R^8 is H, $-CONH_2$, $-NR^9R^{10}$, -CN or phenyl where R^9 and R^{10} are independently $-(C_1-C_4)$alkyl or -phenyl(C_1-C_4)alkyl and n is 1 to 8;

R^4 is H, $-(C_5-C_{14})$alkyl, $-(C_3-C_{14})$cycloalkyl, pyridyl, phenyl or phenyl substituted with $-(C_1-C_6)$alkyl, halo, $-CF_3$, $-OCF_3$, $-(C_1-C_4)$alkoxy, -CN, $-(C_1-C_4)$alkylthio, phenyl(C1-C_4)alkyl, $-(C_1-C_4)$alkylphenyl, phenyl, phenoxy or naphthyl;

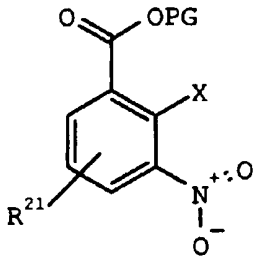
or a pharmaceutically acceptable racemate, solvate, tautomer, optical isomer, prodrug derivative or salt, thereof which process comprises the steps of:

a) esterifying a compound of formula XVI



XVI

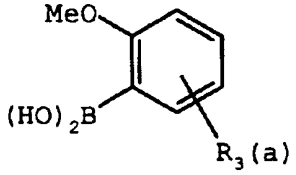
where X is halo to form a compound of formula XV



XV

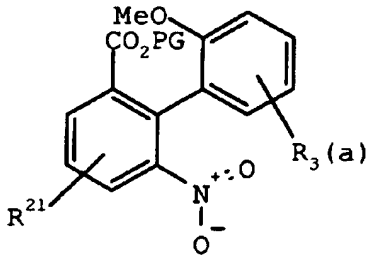
where PG is an acid protecting group;

b) condensing a compound of formula XV with a compound of formula XVII



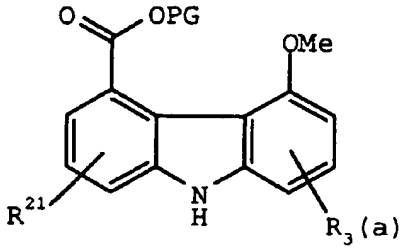
XVII ;

to form a compound of formula XVIII



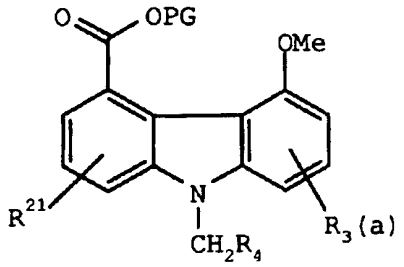
XVIII

c) cyclizing a compound of formula XVIII to form a compound of formula XIX.



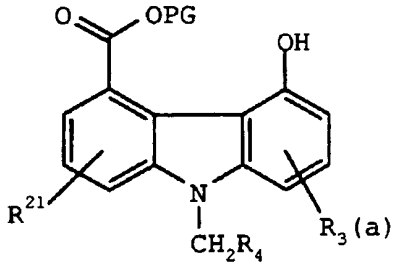
XIX ;

d) alkylating a compound of formula XIX with an alkylating agent of the formula XCH_2R^4, where X is halo, to form a compound of formula XX



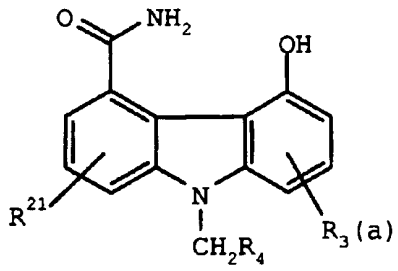
XX ;

e) dealkylating a compound of formula XX to form a compound of formula IX



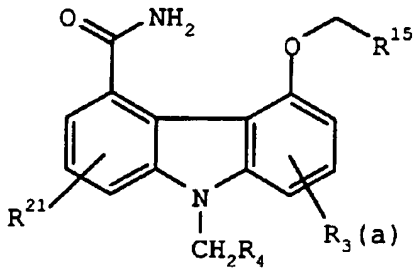
IX

f) aminating compound of formula IX to form a compound of formula VIII



VIII

g) alkylating a compound of formula VIII with an alkylating agent of formula XCH_2R^{15}, where X is halo and R^{15} is $-CO_2R^{16}$, $-SO_3R^{16}$, $P(O)(OR^{16})_2$, or $-P(O)(OR^{16})H$, where R^{16} is an acid protecting group to form a compound of formula VII



VII

h) optionally hydroyzing a compound of formula VII to form a compound of formula I and optionally salifying a compound of formula I.

43. A compound which is selected from the group consisting of ;

(3-Carbomethoxy-2-bromoanilino)-5-methyl-cyclohex-2-en-1-one;

5-Carbomethoxy-1,2-dihydro-2-methyl-9H-carbazol-4(3H)-one;

9-Benzyl-5,7-dimethoxy-1,2,3,4-tetrahydrocarbazole-4-carboxamide;

9-Benzyl-5-hydroxy-7-methoxy-1,2,3,4-tetrahydrocarbazole-4-carboxamide;

[9-Benzyl-4-carbamoyl-7-methoxy-1,2,3,4-tetrahydrocarbazol-5-yl]oxyacetic acid, ethyl ester;

9-Benzyl-4-carbamoyl-5,7-dimethoxycarbazole;

9-Benzyl-4-carbamoyl-5-hydroxy-7-methoxycarbazole;

[9-Benzyl-4-carbamoyl-7-methoxycarbazol-5-yl]oxyacetic acid, methyl ester;

[(2,9-Bis-benzyl-4-carbamoyl-1,2,3,4-tetrahydro-beta-carbazol-5-yl)oxy]acetic acid, ethyl ester;

(3-Carbomethoxy-2-bromoanilino)-5-methyl-cyclohex-2-en-1-one;

5-Carbomethoxy-1,2-dihydro-2-methyl-9H-carbazol-4(3H)-one;

[(Phenyl)methyl]-5-carbomethoxy-2-methyl-1,2-dihydrocarbazol-4(3H)-one;

[(Phenyl)methyl]-2-methyl-4-hydroxy-5-carbomethoxy carbazole;

[(Phenyl)methyl]-2-methyl-4-hydroxy-5-carbamoyl carbazole;

[(Phenyl)methyl]-2-methyl-5-carbamoylcarbazol-4-yl}oxyacetic acid, methyl ester;

[(3-Fluorophenyl)methyl]-5-carbomethoxy-2-methyl-1,2-dihydrocarbazol-4(3H)-one;

[(3-Fluorophenyl)methyl]-2-methyl-4-hydroxy-5-carbomethoxy carbazole;

[(3-Fluorophenyl)methyl]-2-methyl-4-hydroxy-5-carbamoyl carbazole;

[(3-Fluorophenyl)methyl]-2-methyl-5-carbamoylcarbazol-4-yl}oxyacetic acid, methyl ester;

[(3-Methylphenyl)methyl]-5-carbomethoxy-2-methyl-1,2-dihydrocarbazol-4(3H)-one;

[(3-Methylphenyl)methyl]-2-methyl-4-hydroxy-5-carbomethoxy carbazole;

[(3-Methylphenyl)methyl]-2-methyl-4-hydroxy-5-carbamoyl carbazole;

[(3-Methylphenyl)methyl]-2-methyl-5-carbamoylcarbazol-4-yl}oxyacetic acid, methyl ester;

(3-Carbomethoxy-2-bromoanilino)-5-(4-trifluoromethylphenyl-cyclohex-2-en-1-one;

5-Carbomethoxy-1,2-dihydro-2-(4-trifluoromethylphenyl)-9H-carbazol-4(3H)-one;

[(Phenyl)methyl]-5-carbomethoxy-2-(4-trifluoromethylphenyl)-1,2-dihydrocarbazol-4(3H)-one;

[(Phenyl)methyl]-2-(4-trifluoromethylphenyl)-4-hydroxy-5-carbomethoxy carbazole;

[(Phenyl)methyl]-2-(4-trifluoromethylphenyl)-4-hydroxy-5-carbamoyl carbazole;

[(Phenyl)methyl]-2-(4-trifluoromethylphenyl)-5-carbamoylcarbazol-4-yl}oxyacetic acid, methyl ester;

(2-Bromo-3-carbomethoxyanilino)-5-pentylcyclohex-2-en-1-one;

5-Carbomethoxy-1,2-dihydro-2-pentyl-9H-carbazol-4(3H)-one;

5-Carbomethoxy-1,2-dihydro-2-pentyl-9-(phenylmethyl)carbazol-4(3H)-one;

5-Carbomethoxy-4-hydroxy-2-pentyl-9-(phenylmethyl)carbazole;

5-Carbamoyl-4-hydroxy-2-pentyl-9-(phenylmethyl)carbazole;

[5-Carbamoyl-2-pentyl-9-(phenylmethyl)carbazol-4-yl]oxyacetic acid, methyl ester;

(2-Bromo-3-carbomethoxyanilino)-5-[(1-methyl)ethyl]cyclohex-2-en-1-one;

5-Carbomethoxy-1,2-dihydro-2-(1-methylethyl)-9H-carbazol-4(3H)-one;

5-Carbomethoxy-1,2-dihydro-2-(1-methylethyl)-9-(phenylmethyl)carbazol-4(3H)-one;

5-Carbomethoxy-4-hydroxy-2-(1-methylethyl)-9-(phenylmethyl)carbazole;

5-Carbamoyl-4-hydroxy-2-(1-methylethyl)-9-(phenylmethyl)carbazole;

[5-Carbamoyl-2-(1-methylethyl)-9-(phenylmethyl)carbazol-4-yl]oxyacetic acid, methyl ester;

(2-Bromo-3-carbomethoxyanilino)-5-(hydroxymethyl)cyclohex-2-en-1-one;

5-Carbomethoxy-1,2-dihydro-2-(hydroxymethyl)-9H-carbazol-4(3H)-one;

5-Carbomethoxy-1,2-dihydro-2-(hydroxymethyl)-9-(phenylmethyl)carbazol-4(3H)-one;

[5-Carbamoyl-9-(phenylmethyl)-2-[(tri(-1-methylethyl)silyl)oxymethyl]carbazol-4-yl]oxyacetic acid, methyl ester;

(2-Bromo-3-carbomethoxyanilino)-5-phenylcyclohex-2-en-1-one;

5-Carbomethoxy-1,2-dihydro-2-phenyl-9H-carbazol-4(3H)-one;

5-Carbomethoxy-1,2-dihydro-2-phenyl-9-(phenylmethyl)carbazol-4(3H)-one;

5-Carbomethoxy-4-hydroxy-2-phenyl-9-(phenylmethyl)carbazole;

5-Carbamoyl-4-hydroxy-2-phenyl-9-(phenylmethyl)carbazole;

[5-Carbamoyl-2-phenyl-9-(phenylmethyl)carbazol-4-yl]oxyacetic acid, methyl ester;

(2-Bromo-3-carbomethoxyanilino)-5-(4-chlorophenyl)cyclohex-2-en-1-one;

5-Carbomethoxy-1,2-dihydro-2-(4-chlorophenyl)-9H-carbazol-4(3H)-one;

5-Carbomethoxy-1,2-dihydro-2-(4-chlorophenyl)- 9-(phenylmethyl)carbazol-4(3H)-one;

5-Carbomethoxy-2-(4-chlorophenyl)-4-hydroxy-9-(phenylmethyl)carbazole;

5-Carbamoyl-2-(4-chlorophenyl)-4-hydroxy-9-(phenylmethyl)carbazole;

[5-Carbamoyl-2-(4-chlorophenyl)-9-(phenylmethyl)carbazol-4-yl]oxyacetic acid, methyl ester;

(2-Bromo-3-carbomethoxyanilino)-5-(2-furyl)cyclohex-2-en-1-one;

5-Carbomethoxy-1,2-dihydro-2-(2-furyl)-9H-carbazol-4(3H)-one;

5-Carbomethoxy-1,2-dihydro-2-(2-furyl)- 9-(phenylmethyl)carbazol-4(3H)-one;

5-Carbomethoxy-2-(2-furyl)-4-hydroxy-9-(phenylmethyl)carbazole;

5-Carbamoyl-2-(2-furyl)-4-hydroxy-9-(phenylmethyl)carbazole;

[5-Carbamoyl-2-(2-furyl)-9-(phenylmethyl)carbazol-4-yl]oxyacetic acid, methyl ester;5-Carbomethoxy-1,2-

dihydro-9-(phenylmethyl)-2-[(tri(-1-methylethyl)silyl)oxymethyl]carbazol-4(3H)-one;

5-Carbomethoxy-4-hydroxy-9-(phenylmethyl)-2-[(tri(-1-methylethyl)silyl)oxymethyl]carbazole;

5-Carbamoyl-4-hydroxy-9-(phenylmethyl)-2-[(tri(-1-methylethyl)silyl)oxymethyl]carbazole;

[5-Carbamoyl-9-(phenylmethyl)-2-[(tri(-1-methylethyl)silyl)oxymethyl]carbazol-4-yl]oxyacetic acid, methyl ester;

(3-Carbomethoxy-2-chloroanilino)cyclohex-2-en-1-one;

5-Carbomethoxy-1,2-dihydro-9H-carbazol-4(3H)-one;

(3-Carbomethoxy-2-bromoanilino)cyclohex-2-en-1-one;

[(Phenyl)methyl]-5-carbomethoxy-1,2-dihydrocarbazol-4(3H)-one;

[(Phenyl)methyl]-4-hydroxy-5-carbomethoxy carbazole

[(Phenyl)methyl]-4-hydroxy-5-carbamoyl carbazole;

[(Phenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, methyl ester;

[(3-Fluorophenyl)methyl]-5-carbomethoxy-1,2-dihydrocarbazol-4(3H)-one;

[(3-Fluorophenyl)methyl]-4-hydroxy-5-carbomethoxy carbazole;

[(3-Fluorophenyl)methyl]-4-hydroxy-5-carbamoyl carbazole;

[(3-Fluorophenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, tert-butyl ester;

[(3-Chlorophenyl)methyl]-5-carbomethoxy-1,2-dihydrocarbazol-4(3H)-one;

[(3-Chlorophenyl)methyl]-4-hydroxy-5-carbomethoxy carbazole;

[(3-Chlorophenyl)methyl]-4-hydroxy-5-carbamoyl carbazole;

[(3-Chlorophenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, tert-butyl ester;

[(3-Phenoxyphenyl)methyl]-5-carbomethoxy-1,2-dihydrocarbazol-4(3H)-one;

[(3-Phenoxyphenyl)methyl]-4-hydroxy-5-carbomethoxy carbazole;

[(3-Phenoxyphenyl)methyl]-4-hydroxy-5-carbamoyl carbazole;
[(3-Phenoxyphenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, tert-butyl ester;
[(2-Fluorophenyl)methyl]-5-carbomethoxy-1,2-dihydrocarbazol-4(3H)-one;
[(2-Fluorophenyl)methyl]-4-hydroxy-5-carbomethoxy carbazole;
[(2-Fluorophenyl)methyl]-4-hydroxy-5-carbamoyl carbazole;
[(2-Fluorophenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, methyl ester;
[(2-Trifluoromethylphenyl)methyl]-5-carbomethoxy-1,2-dihydrocarbazol-4(3H)-one;
[(2-Trifluoromethylphenyl)methyl]-4-hydroxy-5-carbomethoxy carbazole;
[(2-Trifluoromethylphenyl)methyl]-4-hydroxy-5-carbamoyl carbazole;
[(2-Trifluoromethylphenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, methyl ester;
[(2-Benzylphenyl)methyl]-5-carbomethoxy-1,2-dihydrocarbazol-4(3H)-one;
[(2-Benzylphenyl)methyl]-4-hydroxy-5-carbomethoxy carbazole;
[(2-Benzylphenyl)methyl]-4-hydroxy-5-carbamoyl carbazole;
[(2-Benzylphenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, methyl ester
[(3-Trifluoromethylphenyl)methyl]-5-carbomethoxy-1,2-dihydrocarbazol-4(3H)-one;
[(3-Trifluoromethylphenyl)methyl]-4-hydroxy-5-carbomethoxy carbazole;
[(3-Trifluoromethylphenyl)methyl]-4-hydroxy-5-carbamoyl carbazole;
[(3-Trifluoromethylphenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, methyl ester;
[(1-Naphthyl)methyl]-5-carbomethoxy-1,2-dihydrocarbazol-4(3H)-one;
[(1-Naphthyl)methyl]-4-hydroxy-5-carbomethoxy carbazole;

[(1-Naphthyl)methyl]-4-hydroxy-5-carbamoyl ;
[(1-Naphthyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, methyl ester;
[(2-Cyanophenyl)methyl]-5-carbomethoxy-1,2-dihydrocarbazol-4(3H)-one;
[(2-Cyanophenyl)methyl]-4-hydroxy-5-carbomethoxy carbazole;
[(2-Cyanophenyl)methyl]-4-hydroxy-5-carbamoyl carbazole;
[(2-Cyanophenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, methyl ester;
[(3-Cyanophenyl)methyl]-5-carbomethoxy-1,2-dihydrocarbazol-4(3H)-one;
[(3-Cyanophenyl)methyl]-4-hydroxy-5-carbomethoxy carbazole;
[(3-Cyanophenyl)methyl]-4-hydroxy-5-carbamoyl carbazole;
[(3-Cyanophenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, tert-butyl ester;
[(2-Methylphenyl)methyl]-5-carbomethoxy-1,2-dihydrocarbazol-4(3H)-one;
[(2-Methylphenyl)methyl]-4-hydroxy-5-carbomethoxy carbazole;
[(2-Methylphenyl)methyl]-4-hydroxy-5-carbamoyl carbazole;
[(2-Methylphenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, methyl ester;
[(3-Methylphenyl)methyl]-5-carbomethoxy-1,2-dihydrocarbazol-4(3H)-one;
[(3-Methylphenyl)methyl]-4-hydroxy-5-carbomethoxy carbazole;
[(3-Methylphenyl)methyl]-4-hydroxy-5-carbamoyl carbazole;
[(3-Methylphenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, methyl ester;
[(3,5-Dimethylphenyl)methyl]-5-carbomethoxy-1,2-dihydrocarbazol-4(3H)-one;
[(3,5-Dimethylphenyl)methyl]-4-hydroxy-5-carbomethoxy carbazole;
[(3,5-Dimethylphenyl)methyl]-4-hydroxy-5-carbamoyl ;
[(3,5-Dimethylphenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, methyl ester;

[(3-Iodophenyl)methyl]-5-carbomethoxy-1,2-dihydrocarbazol-4(3H)-one;

[(3-Iodophenyl)methyl]-4-hydroxy-5-carbomethoxy carbazole;

[(3-Iodophenyl)methyl]-4-hydroxy-5-carbamoyl carbazole;

[(3-Iodophenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, methyl ester;

[(2-Chlorophenyl)methyl]-5-carbomethoxy-1,2-dihydrocarbazol-4(3H)-one;

[(2-Chlorophenyl)methyl]-4-hydroxy-5-carbomethoxy carbazole;

[(2-Chlorophenyl)methyl]-4-hydroxy-5-carbamoyl carbazole;

[(2-Chlorophenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, tert-butyl ester;

[(2,3-Difluorophenyl)methyl]-5-carbomethoxy-1,2-dihydrocarbazol-4(3H)-one;

[(2,3-Difluorophenyl)methyl]-4-hydroxy-5-carbomethoxy carbazol;

[(2,3-Difluorophenyl)methyl]-4-hydroxy-5-carbamoyl carbazole;

[(2,3-Difluorophenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, methyl ester;

[(2,6-Difluorophenyl)methyl]-5-carbomethoxy-1,2-dihydrocarbazol-4(3H)-one

[(2,6-Difluorophenyl)methyl]-4-hydroxy-5-carbomethoxy carbazole;

[(2,6-Difluorophenyl)methyl]-4-hydroxy-5-carbamoyl ;

[(2,6-Difluorophenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, methyl ester;

[(2,6-Dichlorophenyl)methyl]-5-carbomethoxy-1,2-dihydrocarbazol-4(3H)-one;

[(2,6-Dichlorophenyl)methyl]-4-hydroxy-5-carbomethoxy carbazole;

[(2,6-Dichlorophenyl)methyl]-4-hydroxy-5-carbamoyl carbazole;

[(2,6-Dichlorophenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, methyl ester;

[(3-Trifluoromethoxyphenyl)methyl]-5-carbomethoxy-1,2-dihydrocarbazol-4(3H)-one;

[(3-Trifluoromethoxyphenyl)methyl]-4-hydroxy-5-carbomethoxy carbazole;

[(3-Trifluoromethoxyphenyl)methyl]-4-hydroxy-5-carbamoyl carbazole;

[(3-Trifluoromethoxyphenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, methyl ester;

2-Carbomethoxy-6-nitro-2'-methoxy-biphenyl;

9H-4-methoxy-5-carbomethoxy carbazole;

[(2-Biphenyl)methyl]-4-methoxy-5-carbomethoxy carbazole;

[(2-Biphenyl)methyl]-4-hydroxy-5-carbomethoxy carbazole;

[(2-Biphenyl)methyl]-4-hydroxy-5-carbamoyl carbazole;

[(2-Biphenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, tert-butyl ester;

[(2-Biphenyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, methyl ester;

9-Benzyl-4-carboxy-5-methoxy-1,2,3,4-tetrahydrocarbazole, ethyl ester;

9-Benzyl-4-carbamoyl-5-hydroxy-1,2,3,4-tetrahydrocarbazole;

9-benzyl-4-carboxy-5-hydroxy-1,2,3,4-tetrahydrocarbazole, ethyl ester ;

[9-Benzyl-4-carbamoyl-1,2,3,4-tetrahydrocarbaole-5-yl]oxyacetic acid, methyl ester;

[(2-Pyridyl)methyl]-5-carbomethoxy-1,2-dihydrocarbazol-4(3H)-one;

[(2-Pyridyl)methyl]-4-hydroxy-5-carbomethoxy carbazole;

[(2-Pyridyl)methyl]-4-hydroxy-5-carbamoyl carbazole;

[(2-Pyridyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, methyl ester;

[(3-Pyridyl)methyl]-5-carbomethoxy-1,2-dihydrocarbazol-4(3H)-one;

[(3-Pyridyl)methyl]-4-hydroxy-5-carbomethoxy carbazole;

[(3-Pyridyl)methyl]-4-hydroxy-5-carbamoyl carbazole;

[(3-Pyridyl)methyl]-5-carbamoylcarbazol-4-yl}oxyacetic acid, methyl ester;

Ethyl 5-methoxy-8-methyl-1,2,3,4-tetrahydrocarbazole-4-carboxylate;

Ethyl 9-benzyl-5-methoxy-8-methyl-1,2,3,4-tetrahydrocarbazole-4-carboxylate;

9-Benzyl-5-methoxy-8-methyl-1,2,3,4-tetrahydrocarbazole-4-carboxamide;

9-Benzyl-5-hydroxy-8-methyl-1,2,3,4-tetrahydrocarbazole-4-carboxamide;

[9-Benzyl-4-carbamoyl-8-methyl-1,2,3,4-tetrahydrocarbazol-5-yl]oxyacetic acid methyl;

5-Carbamoyl-4-methoxy-1-methylcarbazole;

9-Benzyl-5-carbamoyl-4-methoxy-1-methylcarbazole;

9-Benzyl-5-carbamoyl-4-hydroxy-1-methylcarbazole;

[9-Benzyl-5-carbamoyl-1-methylcarbazol-4-yl]oxyacetic acid, methyl;

Ethyl 9-benzyl-5-methoxy-8-fluoro-1,2,3,4-tetrahydrocarbazole-4-carboxylate;

9-Benzyl-5-methoxy-8-fluoro-1,2,3,4-tetrahydrocarbazole-4-carboxamide;

9-Benzyl-5-hydroxy-8-fluoro-1,2,3,4-tetrahydrocarbazole-4-carboxamide;

[9-Benzyl-4-carbamoyl-8-fluoro-1,2,3,4-tetrahydrocarbazol-5-yl]oxyacetic acid methyl ester ;

9-Benzyl-5-carbamoyl-4-methoxy-1-fluorocarbazole;

9-Benzyl-5-carbamoyl-4-hydroxy-1-fluorocarbazole;

[9-Benzyl-5-carbamoyl-1-fluorocarbazol-4-yl]oxyacetic acid methyl ester ;

Ethyl 9-benzyl-5-methoxy-8-chloro-1,2,3,4-tetrahydrocarbazole-4-carboxylate;

9-Benzyl-5-methoxy-8-chloro-1,2,3,4-tetrahydrocarbazole-4-carboxamide;

9-Benzyl-5-hydroxy-8-chloro-1,2,3,4-tetrahydrocarbazole-4-carboxamide;

[9-Benzyl-4-carbamoyl-8-chloro-1,2,3,4-tetrahydrocarbazol-5-yl]oxyacetic acid methyl ester;

9-Benzyl-5-carbamoyl-4-methoxy-1-chlorocarbazole;

5-Carbamoyl-4-hydroxy-1-chlorocarbazole;

[5-Carbamoyl-1-chlorocarbazol-4-yl]oxyacetic acid methyl ester

[9-Benzyl-5-carbamoyl-1-chlorocarbazol-4-yl]oxyacetic acid methyl ester;

[(Cyclohexyl)methyl]-5-carbomethoxy-1,2-dihydrocarbazol-4(3H)-one;

[(Cyclohexyl)methyl]-4-hydroxy-5-carbomethoxy carbazole;

[(Cyclohexyl)methyl]-4-hydroxy-5-carbamoyl carbazole;

[(Cyclohexyl)methyl]-5-carbamoylcarbazol-4-yl]oxyacetic acid, methyl ester;

[(Cyclopentyl)methyl]-5-carbomethoxy-1,2-dihydrocarbazol-4(3H)-one;

[(Cyclopentyl)methyl]-4-hydroxy-5-carbamoyl carbazole

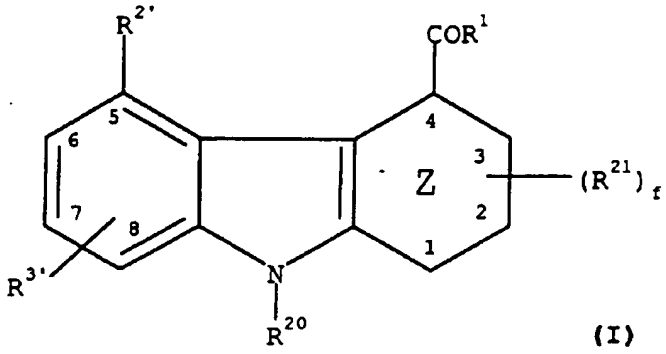
[(Cyclopentyl)methyl]-5-carbamoylcarbazol-4-yl]oxyacetic acid, methyl ester;

or a pharmaceuticallt acceptable racemate, solvate, tautomer, optical isomer, prodrug derivative or salt thereof.

44. The use of a compound as claimed in any one of **Claims 1-23** for the manufacture of a medicament for the treatment of sepsis, septic shock, adult respiratory distress syndrome, pancreatitis, trauma-induced shock, bronchial asthma, allergic rhinitis, rheumatoid arthritis, cystic fibrosis, stroke, acute bronchitis, chronic bronchitis, acute bronchiolitis, chronic bronchiolitis,

osteoarthritis, gout, spondylarthropathris, ankylosing spondylitis, Reiter's syndrome, psoriatic arthropathy, enterapathric spondylitis, Juvenile arthropathy or juvenile ankylosing spondylitis, Reactive arthropathy, infectious or post-infectious arthritis, gonoccocal arthritis, Tuberculous arthritis, viral arthritis, fungal arthritis, syphilitic arthritis, Lyme disease, arthritis associated with "vasculitic syndromes", polyarteritis nodosa, hypersensitivity vasculitis, Luegenec's granulomatosis, polymyalgin rheumatica, joint cell arteritis, calcium crystal deposition arthropathris, pseudo gout, non-articular rheumatism, bursitis, tenosynomitis, epicondylitis (tennis elbow), carpal tunnel syndrome, repetitive use injury (typing), miscellaneous forms of arthritis, neuropathic joint disease (charco and joint), hemarthrosis (hemarthrosic), Henoch-Schonlein Purpura, hypertrophic osteoarthropathy, multicentric reticulohistiocytosis, arthritis associated with certain diseases, surcoilosis, hemochromatosis, sickle cell disease and other hemoglobinopathries, hyperlipoproteineimia, hypogammaglobulinemia, hyperparathyroidism, acromegaly, familial Mediterranean fever, Behat's Disease, systemic lupus erythrematosis, or relapsing polychondritis; and related diseases which comprises administering to a mammal in need of such treatment a therapeutically effective amount of a compound of formula I or formula II.

45. The use of a pharmaceutically effective amount of a compound of formula (I)



(I)

wherein;

Z is cyclohexenyl, or phenyl,

R^{20} is selected from groups (a), (b) and (c) where;

(a) is -(C5-C20)alkyl, -(C5-C20)alkenyl, -(C5-C20)alkynyl, carbocyclic radicals, or heterocyclic radicals, or

(b) is a member of (a) substituted with one or more independently selected non-interfering substituents; or

(c) is the group $-(L)-R^{80}$; where, (L)-is a divalent linking group of 1 to 12 atoms selected from carbon, hydrogen, oxygen, nitrogen, and sulfur; wherein the combination of atoms in -(L)- are selected from the group consisting of (i) carbon and hydrogen only, (ii) one sulfur only, (iii) one oxygen only, (iv) one or two nitrogen and hydrogen only, (v) carbon, hydrogen, and one sulfur only, and (vi) an carbon, hydrogen, and oxygen only; and where R^{80} is a group selected from (a) or (b);

R^{21} is a non-interfering substituent where f is 1-3;

R^1 is $-NHNH_2$, $-NH_2$, or $-CONH_2$;

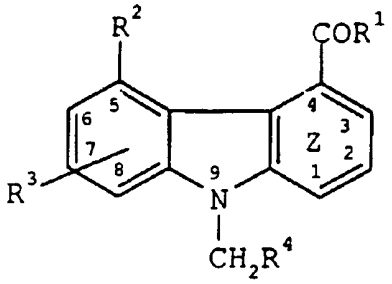
$R^{2'}$ is selected from the group consisting of -OH, and $-O(CH_2)_tR^{5'}$ where

$R^{5'}$ is H, -CN, $-NH_2$, $-CONH_2$, $-CONR^9R^{10}$ $-NHSO_2R^{15}$; $-CONHSO_2R^{15}$, where R^{15} is $-(C_1-C_6)$alkyl or $-CF_3$; phenyl or phenyl substituted with $-CO_2H$ or $-CO_2(C_1-C_4)$alkyl; and $-(L_a)-$(acidic group), wherein $-(L_a)-$ is an acid linker having an acid linker length of 1 to 7 and t is 1-5;

$R^{3'}$ is selected from non-interfering substituent, carbocyclic radicals, carbocyclic radicals substituted with non-interfering substituents, heterocyclic radicals, and heterocyclic radicals substituted with non-interfering substituents;

or a pharmaceutically acceptable racemate, solvate, tautomer, optical isomer, prodrug derivative or salt, thereof for selectively inhibiting $sPLA_2$ in a mammal in need of such treatment.

46. The use of a therapeutically effective amount of a compound of formula (II)



(II)

wherein;

R^1 is $-NHNH_2$, or $-NH_2$;

R^2 is selected from the group consisting of -OH and $-O(CH_2)_mR^5$ where

R^5 is H, $-CO_2H$, $-CONH_2$, $-CO_2(C_1-C_4$ alkyl); $-\overset{O}{\overset{\|}{P}}(R^6R^7)$, where R^6 and R^7 are each independently -OH or $-O(C_1-C_4)$alkyl; $-SO_3H$, $-SO_3$(C1-C4 alkyl), tetrazolyl, -CN, $-NH_2$, $-NHSO_2R^{15}$; $-CONHSO_2R^{15}$, where R^{15} is $-(C_1-C_6)$alkyl or $-CF_3$, phenyl or phenyl substituted with $-CO_2H$ or $-CO_2(C_1-C_4)$alkyl where m is 1-3;

R^3 is H, $-O(C_1-C_4)$alkyl, halo, $-(C_1-C_6)$alkyl, phenyl, $-(C_1-C_4)$alkylphenyl; phenyl substituted with $-(C_1-C_6)$alkyl, halo, or $-CF_3$; $-CH_2OSi(C_1-C_6)$alkyl, furyl, thiophenyl, $-(C_1-C_6)$hydroxyalkyl; or $-(CH_2)_nR^8$ where R^8 is H, $-CONH_2$, $-NR^9R^{10}$, -CN or phenyl where R^9 and R^{10} are independently $-(C_1-C_4)$alkyl or -phenyl(C_1-C_4)alkyl and n is 1 to 8;

R^4 is H, $-(C_5-C_{14})$alkyl, $-(C_3-C_{14})$cycloalkyl, pyridyl, phenyl or phenyl substituted with $-(C_1-C_6)$alkyl, halo, $-CF_3$, $-OCF_3$, $-(C_1-C_4)$alkoxy, -CN, $-(C_1-C_4)$alkylthio, phenyl(C1-C4)alkyl, $-(C_1-C_4)$alkylphenyl, phenyl, phenoxy or naphthyl;

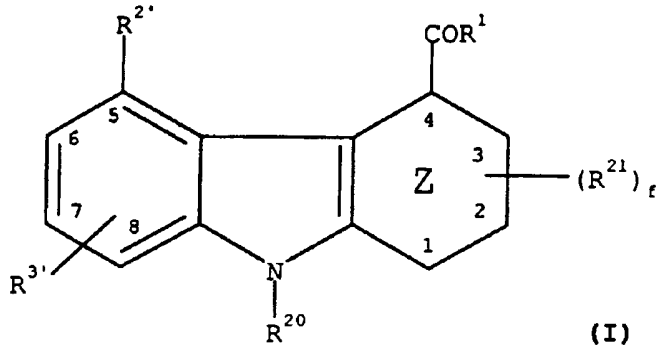
Z is cyclohexenyl, or phenyl;

or a pharmaceutically acceptable racemate, solvate, tautomer, optical isomer, prodrug derivative or salt, thereof for selectively inhibiting $sPLA_2$ in a mammal in need of such treatment.

47. The use as claimed in any one of **Claims 45 or 46** wherein the mammal is a human.

48. The use of a compound of formula I as claimed in any one of **Claims 1-23** in an amount sufficient to inhibit $sPLA_2$ mediated release of fatty acid and to thereby inhibit or prevent the arachidonic acid cascade and its deleterious products for alleviating the pathological effects of $sPLA_2$ related diseases in a mammal in need of such treatment.

49. The use of a therapeutically effective amount of a compound of formula I



(I)

wherein;

Z is cyclohexenyl, or phenyl,

R^{20} is selected from groups (a), (b) and (c) where;

(a) is -(C5-C20)alkyl, -(C5-C20)alkenyl, -(C5-C20)alkynyl, carbocyclic radicals, or heterocyclic radicals, or

(b) is a member of (a) substituted with one or more independently selected non-interfering substituents; or

(c) is the group $-(L)-R^{80}$; where, (L)-is a divalent linking group of 1 to 12 atoms selected from carbon, hydrogen, oxygen, nitrogen, and sulfur; wherein the combination of atoms in -(L)- are selected from the group consisting of (i) carbon and hydrogen only,

(ii) one sulfur only, (iii) one oxygen only, (iv) one or two nitrogen and hydrogen only, (v) carbon, hydrogen, and one sulfur only, and (vi) an carbon, hydrogen, and oxygen only; and where R^{80} is a group selected from (a) or (b);

R^{21} is a non-interfering substituent where f is 1-3;

R^1 is $-NHNH_2$, $-NH_2$, or $-CONH_2$;

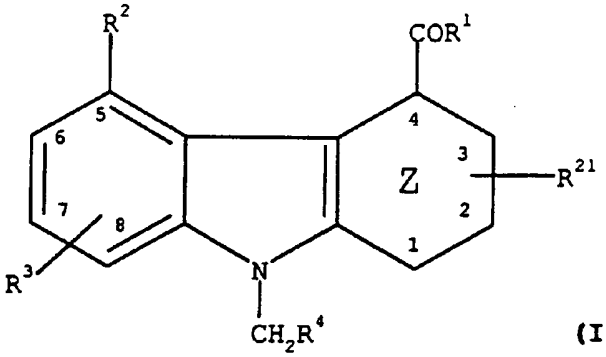
$R^{2'}$ is selected from the group consisting of -OH, and $-O(CH_2)_tR^{5'}$ where

$R^{5'}$ is H, -CN, $-NH_2$, $-CONH_2$, $-CONR^9R^{10}$ $-NHSO_2R^{15}$; $-CONHSO_2R^{15}$, where R^{15} is $-(C_1-C_6)$alkyl or $-CF_3$; phenyl or phenyl substituted with $-CO_2H$ or $-CO_2(C_1-C_4)$alkyl; and $-(L_a)-$(acidic group), wherein $-(L_a)-$ is an acid linker having an acid linker length of 1 to 7 and t is 1-5;

$R^{3'}$ is selected from non-interfering substituent, carbocyclic radicals, carbocyclic radicals substituted with non-interfering substituents, heterocyclic radicals, and heterocyclic radicals substituted with non-interfering substituents;

or a pharmaceutically acceptable racemate, solvate, tautomer, optical isomer, prodrug derivative or salt, thereof for treating sepsis, septic shock, rheumatoid arthritis, osteoarthritis, stroke, apoptosis, asthma, chronic bronchitis, acute bronchitis, cystic fibrosis, inflammatory bowel disease, or pancreatitis in a subject in need of such treatment.

50. The use of a therapeutically effective amount of a compound of formula II



(II)

wherein;

Z is cyclohexenyl, or phenyl,

R^{21} is a non-interfering substituent;

R^1 is $-NHNH_2$ or $-NH_2$;

R^2 is selected from the group consisting of -OH and $-O(CH_2)_mR^5$ where

R^5 is H, $-CO_2H$, $-CONH_2$, $-CO_2(C_1-C_4$ alkyl); $-\overset{O}{\overset{\|}{P}}(R^6R^7)$, where R^6 and R^7 are each independently -OH or $-O(C_1-C_4)$alkyl; $-SO_3H$, $-SO_3$(C1-C4 alkyl), tetrazolyl, -CN, $-NH_2$, $-NHSO_2R^{15}$; $-CONHSO_2R^{15}$, where R^{15} is $-(C_1-C_6)$alkyl or $-CF_3$, phenyl or phenyl substituted with $-CO_2H$ or $-CO_2(C_1-C_4)$alkyl where m is 1-3;

R^3 is H, $-O(C_1-C_4)$alkyl, halo, $-(C_1-C_6)$alkyl, phenyl, $-(C_1-C_4)$alkylphenyl; phenyl substituted with $-(C_1-C_6)$alkyl, halo, or $-CF_3$; $-CH_2OSi(C_1-C_6)$alkyl, furyl, thiophenyl, $-(C_1-C_6)$hydroxyalkyl; or $-(CH_2)_nR^8$ where R^8 is H, $-CONH_2$, $-NR^9R^{10}$, -CN or phenyl where R^9 and R^{10} are independently $-(C_1-C_4)$alkyl or $-$phenyl(C_1-C_4)alkyl and n is 1 to 8;

R^4 is H, -(C_5-C_{14})alkyl, -(C_3-C_{14})cycloalkyl, pyridyl, phenyl or phenyl substituted with -(C_1-C_6)alkyl, halo, -CF_3, -OCF_3, -(C_1-C_4)alkoxy, -CN, -(C_1-C_4)alkylthio, phenyl(C1-C_4)alkyl, -(C_1-C_4)alkylphenyl, phenyl, phenoxy or naphthyl;

or a pharmaceutically acceptable racemate, solvate, tautomer, optical isomer, prodrug derivative or salt, thereof for treating sepsis, septic shock, rheumatoid arthritis, osteoarthritis, stroke, apoptosis, asthma, chronic bronchitis, acute bronchitis, cystic fibrosis, inflammatory bowel disease, or pancreatitis in a subject in need of such treatment.

51. The use as claimed in any one of **Claims 45 or 46** for alleviating the pathological effects of sepsis, septic shock, adult respiratory distress syndrome, pancreatitis, trauma-induced shock, bronchial asthma, allergic rhinitis, rheumatoid arthritis, cystic fibrosis, stroke, acute bronchitis, chronic bronchitis, acute bronchiolitis, chronic bronchiolitis, osteoarthritis, gout, spondylarthropathris, ankylosing spondylitis, Reiter's syndrome, psoriatic arthropathy, enterapathric spondylitis, Juvenile arthropathy or juvenile ankylosing spondylitis, Reactive arthropathy, infectious or post-infectious arthritis, gonoccocal arthritis, Tuberculous arthritis, viral arthritis, fungal arthritis, syphilitic arthritis, Lyme disease, arthritis associated with "vasculitic syndromes", polyarteritis nodosa, hypersensitivity vasculitis, Luegenec's granulomatosis, polymyalgin rheumatica, joint cell arteritis, calcium crystal deposition arthropathris, pseudo gout, non-articular rheumatism, bursitis, tenosynomitis, epicondylitis (tennis elbow), carpal tunnel syndrome, repetitive use injury (typing), miscellaneous forms of

arthritis, neuropathic joint disease (charco and joint), hemarthrosis (hemarthrosic), Henoch-Schonlein Purpura, hypertrophic osteoarthropathy, multicentric reticulohistiocytosis, arthritis associated with certain diseases, surcoilosis, hemochromatosis, sickle cell disease and other hemoglobinopathries, hyperlipoproteineimia, hypogammaglobulinemia, hyperparathyroidism, acromegaly, familial Mediterranean fever, Behat's Disease, systemic lupus erythrematosis, or relapsing polychondritis; and related diseases which comprises administering to a mammal in need of such treatment a therapeutically effective amount of a compound of formula I.